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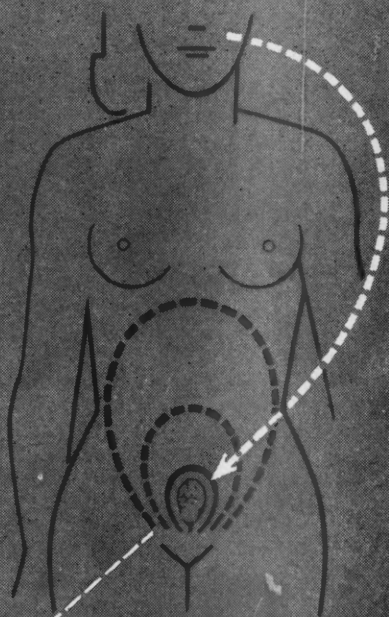
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HABITUAL ABORTION

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¹ Krohn, L., Harris, J. M.: Am. J. Obst. & Gynec. 41:95, 1941.

² Seale, S. D.: Am. J. Obst. & Gynec. 42:1009, 1941.

³ Wenner, R.: Schweiz. med. Wcheschr. 70:417, 1940.

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and Abdominal Surgeons

Fifty-Sixth Annual Meeting, Sept. 7 to 9, 1944

(Concluded)

TOTAL ABDOMINAL HYSTERECTOMY

Observations Based on a Series of 1,925 Patients*

WILLIAM F. MENGERT, M.D., DALLAS, TEXAS, AND

RODNEY STOLTZ, M.D., IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology of the State University of Iowa and the Department of Obstetrics and Gynecology, Southwestern Medical College and Parkland Hospital)

BETWEEN Jan. 1, 1926, and Dec. 31, 1943, 2,820 women underwent some form of hysterectomy at the University of Iowa. In the early years of the present administration of the Department of Obstetrics and Gynecology, subtotal hysterectomy was performed routinely with the total operation reserved for necessity. During 1932, the clinic policy changed; more and more total hysterectomies were elected so that during the next two years, 1933 and 1934, not a single subtotal operation was done. This rigorous policy was relaxed for the next few years, but since 1938 more than 90 per cent and since 1940 more than 95 per cent of all abdominal hysterectomies have included the cervix.

The 2,820 operations included 1,925 total, 393 subtotal, 475 vaginal, and 27 radical (Wertheim) hysterectomies; the year by year distribution is shown in Fig. 1. The purpose of this paper is to detail the experience obtained in performing the 1,925 total abdominal hysterectomies.

The Patient

The women of the series were preponderantly white (94.9 per cent), mostly indigent, and ranged in age from 20 to more than 70 years, with an average of 50 years. Their weights ranged from less than 100 to more than 250 pounds, with an average of 130. Forty per cent

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

had never undergone an abdominal or vaginal operation. Only 326, or 16.9 per cent, were nulliparous, the remainder having had an average of four pregnancies.

Preoperative Course

Fifty-nine per cent of the patients remained in the hospital from two to five days prior to operation, and 27 per cent remained more than six days. Operation within twenty-four hours following admission took place in only 12 per cent. The most common preoperative complications were hypertension and anemia, occurring in 493 and 407 women, respectively, and in association with each other eighty-four times. Fourteen patients suffered from diabetes mellitus and twelve were febrile.

It has always been customary to examine all patients at a group session and only rarely did a patient escape examination by the chief or one of his associates. The accuracy of these preoperative diagnoses was 71.9 per cent. For the sake of greater accuracy, postoperative rather than preoperative diagnoses (Table I) are tabulated. Malignant tumors of the uterus (167) or of the ovary (67) were present 234 times. Since no one would question the necessity of performing total hysterectomy in these conditions, it is obvious that removal of the cervix was demanded in 12.1 per cent, or in 1 patient in 8.

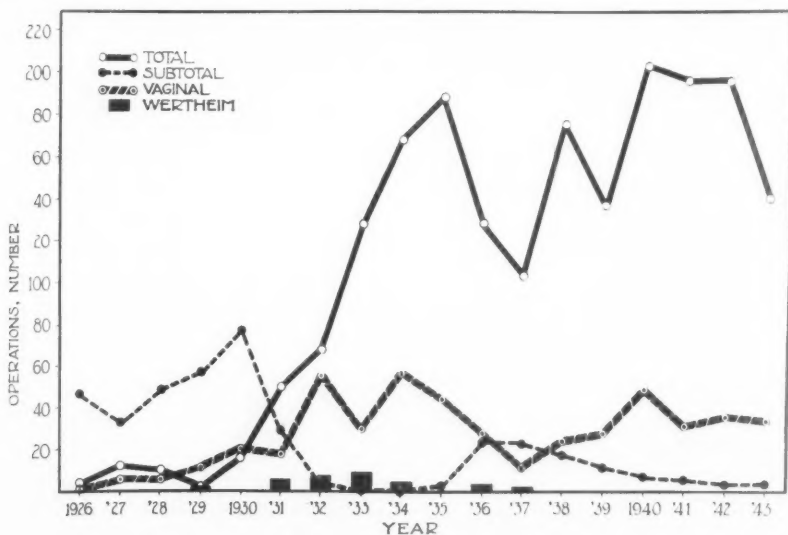


Fig. 1.—Annual incidence of types of hysterectomy.

The Operator

Five senior staff members performed 36 per cent, eighteen senior residents, with assistants usually of lower rank, 39 per cent, and assistant or associate residents, generally assisted by more experienced operators, 475 operations, or 25 per cent. The mortality rates for these three groups, senior staff, senior residents, and others, were 2.9, 2.0, and 0.6 per cent, respectively. This difference is to be expected, since difficult technical procedures and poor risk patients were generally assigned to experienced operators.

The Operation

Since the techniques involved in total hysterectomy will be reported elsewhere, they will be omitted here. Suffice it to say that the vaginal apex was closed or left open, more often the latter, and that no attempt was made in any way to support the vagina with the round, ovarian, or infundibulopelvic ligaments. (Figs. 2-6.)

TABLE I. DIAGNOSES AS DETERMINED DURING AND FOLLOWING OPERATION

| | NUMBER OF PATIENTS | | |
|-----------------------------|--------------------|-------------------------------|-------|
| | SOLE FINDING | ASSOCIATED WITH OTHER LESIONS | TOTAL |
| Fibromyoma of the uterus | 616 | 240 | 856 |
| Benign ovarian tumor | | 64 | |
| Pelvic inflammatory disease | | 55 | |
| Malignant uterine tumor | | 10 | |
| Miscellaneous | | 111 | |
| Functional bleeding | 247 | 125 | 372 |
| Fibromyoma of uterus | | 45 | |
| Benign ovarian tumor | | 30 | |
| Miscellaneous | | 50 | |
| Pelvic inflammatory disease | 172 | 157 | 329 |
| Fibromyoma of uterus | | 55 | |
| Functional bleeding | | 31 | |
| Benign ovarian tumor | | 30 | |
| Miscellaneous | | 41 | |
| Benign ovarian tumor | 150 | 168 | 318 |
| Fibromyoma of uterus | | 64 | |
| Pelvic inflammatory disease | | 30 | |
| Functional bleeding | | 21 | |
| Miscellaneous | | 53 | |
| Malignant uterine tumor | 133 | 34 | 167 |
| Fibromyoma of uterus | | 10 | |
| Miscellaneous | | 24 | |
| Malignant ovarian tumor | 48 | 19 | 67 |
| Miscellaneous | | 19 | |
| Miscellaneous diagnoses | 74 | 141 | 215 |

Because of multiplicity of lesions, totals are more than 1,925.

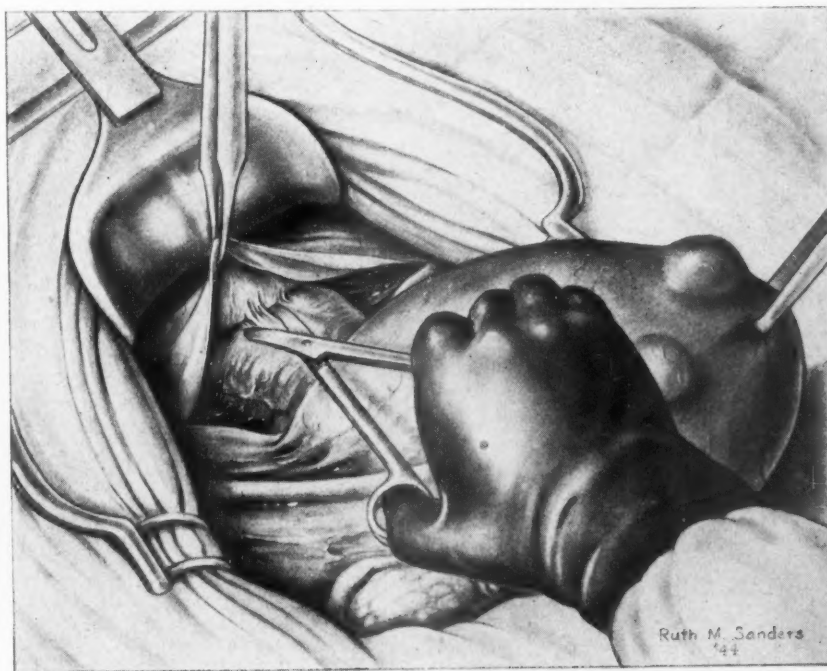


Fig. 2.—Technique of total abdominal hysterectomy—downward dissection of the bladder. The bladder is lifted up with forceps and the cleavage line developed with scissors by a cutting and pushing motion.

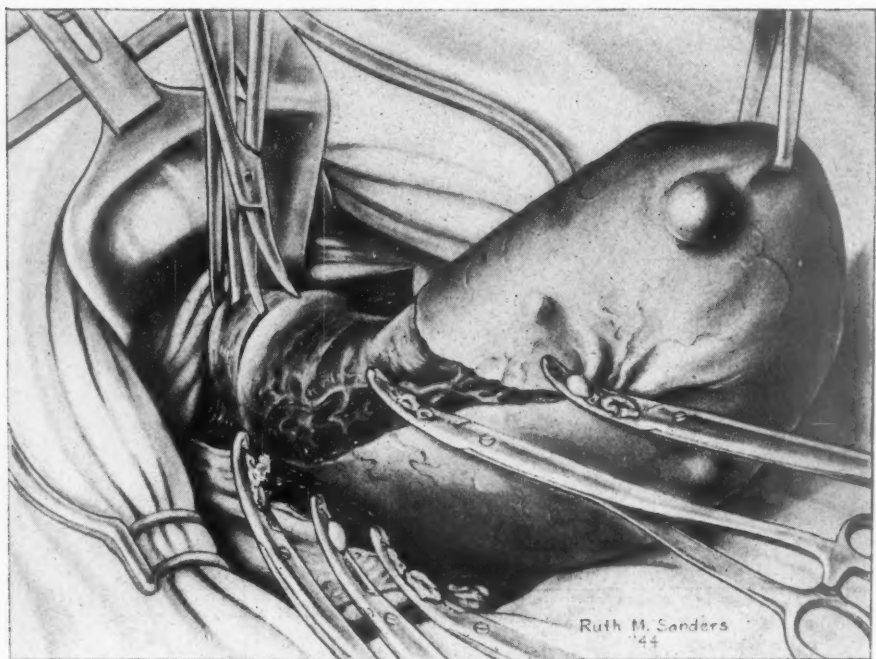


Fig. 3.—Technique of total abdominal hysterectomy. The vagina is opened anteriorly just below the cervix. After opening, a fluffed sponge is tucked into the vagina to absorb fluid left from preoperative vaginal preparation.

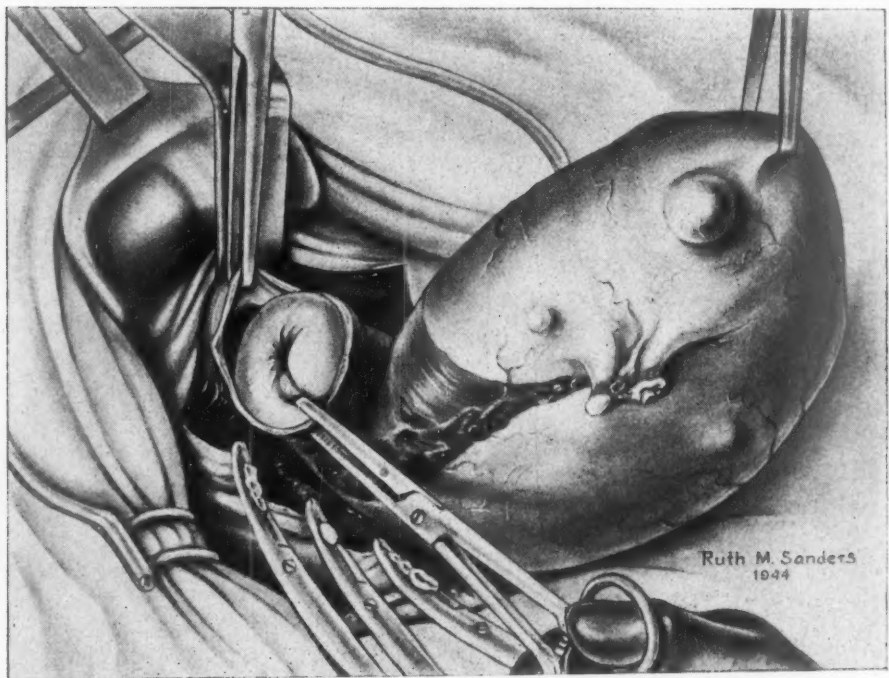


Fig. 4.—Technique of total abdominal hysterectomy. The cervix is retracted with a volsellum forceps and the vagina circumcised under direct vision and as close to the cervix as possible. No special attention is paid to the sacrouterine ligaments although they may be clamped if desired.

TABLE II. ELECTIVE OPERATIONS COMBINED WITH TOTAL HYSTERECTOMY

| | NUMBER OF PATIENTS |
|--------------------------|--------------------|
| Bilateral salpingectomy | 767 |
| Bilateral oophorectomy | 716 |
| Appendectomy | 704 |
| Unilateral oophorectomy | 583 |
| Unilateral salpingectomy | 496 |
| Dilatation and curettage | 150 |
| Vaginal plastic repair | 84 |
| Herniorrhaphy | 54 |
| Miscellaneous | 64 |

Since associated elective operations were frequently multiple, the total is more than 1,925.

Associated elective operations are detailed in Table II and the anesthetics employed are listed in Table III. In no instance was a patient operated upon without anesthesia. During 1943 and the latter part of 1942, injections of a purified extract of curare* were successfully employed with cyclopropane and ethylene anesthesia to relax the abdominal musculature.

Complications, usually of a technical nature, were experienced in 1,013, 53 per cent, of the patients (listed in Table IV) and by and large were relatively minor. On the other hand, it may be significant that twenty-three of the thirty-eight fatalities were recruited from the group of patients with operative complications. Stated differently, this death rate was 2.3 as compared with 1.6 per cent in the uncomplicated group.

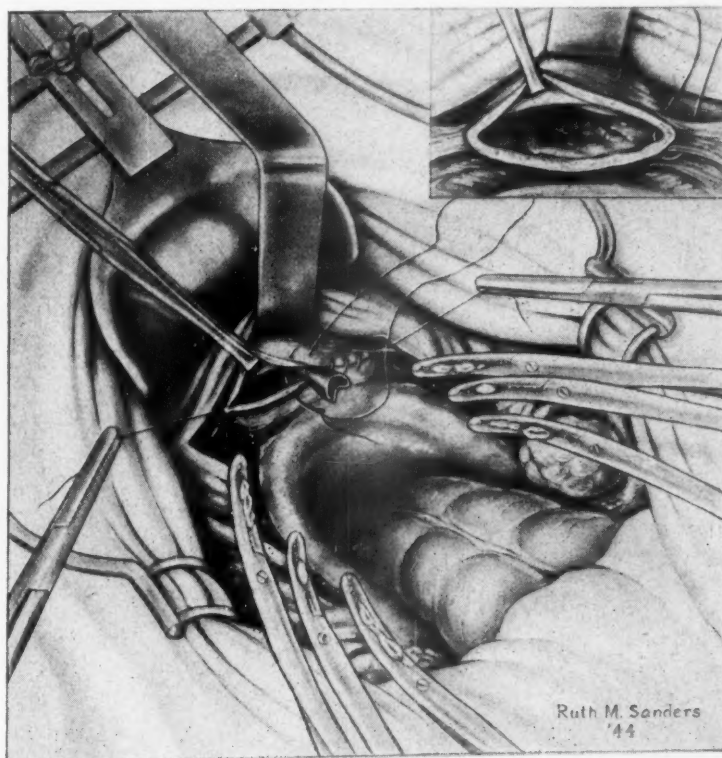


Fig. 5.—Technique of abdominal hysterectomy. The vagina is closed with a continuous whipover stitch of chromic 1 catgut, which includes the whole thickness of vaginal mucosa and the fascia propria of both the anterior and posterior walls. Since the sacrouterine ligaments are part of the posterior fascia propria, they are included in this suture. A soft rubber drain, removed the next morning, is left in situ to provide vaginal drainage for any bleeding. Optionally, the vagina may be left wide open. In this event, the edges must be whipped over with interrupted or continuous sutures in order to effect hemostasis of the vaginal cuff. Note that the round and ovarian ligaments are not sutured to the vaginal cuff.

Inset: Since vaginal branches of the uterine artery sometimes produce troublesome postoperative bleeding, mattress sutures are placed bilaterally.

*Intocostrin (Squibb).

TABLE III. THE ANESTHETIC

| | NUMBER OF TIMES EMPLOYED | | |
|--------------------|-----------------------------|-------|-------------------|
| | TOTAL | ALONE | IN COMBINATION |
| Ether | 1188 | 68 | 1120 |
| Ethylene | 755 | 56 | 699 |
| Nitrous oxide | 482 | 2 | 480 |
| Spinal | 464 | 286 | 178 |
| Cyclopropane | 391 | 269 | 122 |
| Local infiltration | 7 | 1 | 6 |
| Other | 11 | 11 | 0 |

Because of multiple combinations of anesthetics, the sum of column 1 is more than 1,925.

One anesthetic was employed in 693 patients, two in 1,087, three in 144, and four in 1. This total equals 1,925.

TABLE IV. COMPLICATIONS DURING OPERATION

| | TIMES NOTED |
|-------------------------------|-------------|
| Troublesome adhesions | 833 |
| Troublesome bleeding | 115 |
| Shock | 54 |
| Large bowel injury | 12 |
| Ureteral ligation or division | 10 |
| Bladder injury | 12 |

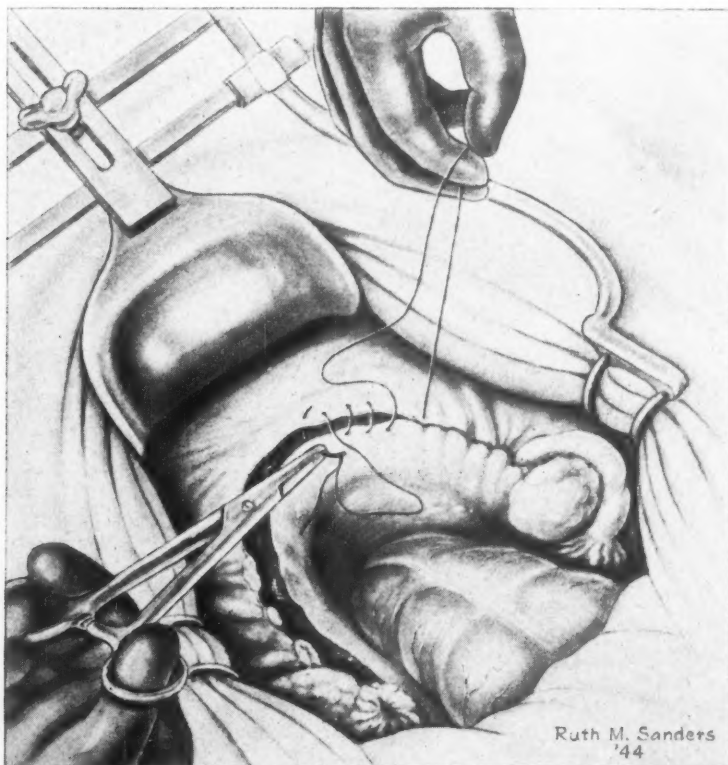


Fig. 6.—Technique of abdominal hysterectomy—peritonization with continuous chromic 00, care being taken to extraperitonize the ovarian and round ligaments and the tubal stumps.

Although the chief complicating factors were adhesions and bleeding, principal concern was associated with large bowel, ureteral, and bladder injuries which occurred twelve, ten, and twelve times, respectively. Our comparative experience suggests that bowel and bladder injury occurs with similar frequency in any type of abdominal hysterectomy. For

example, there were eight bladder injuries in subtotal and twelve in total hysterectomies. Furthermore, the annual incidence of bladder injury was relatively constant. There were six in the first half and six in the second half of the total hysterectomy series. On the other hand, ureteral injury, while not peculiar to, is more frequently associated with total hysterectomy. Such injury may be avoided with accurate anatomic knowledge and careful dissection. Adequate downward displacement of the bladder tends to increase the distance between cervix and ureters. Group experience developing in any clinic with a closely associated staff tends to minimize the frequency of ureteral injury. This point is illustrated by the fact that seven of the ureteral injuries occurred in the first half and three in the second half of the series, incidences of 0.7 and 0.3 per cent, respectively. Some operators at first employed indwelling ureteral catheters in preoperative preparation but tended to discard this technique as they gained experience. The cut ureter was generally reimplanted in the bladder and contributed to death in only one instance. Secondary operation to reimplant the ureter was necessary only once. In general, bladder or ureteral injuries in gynecologic surgery are amenable to correction and heal well if recognized and repaired immediately. The unforgivable sin is failure to recognize the injury before closure of the abdomen. A detailed report of all types of injury during the course of gynecologic operations is in preparation.

Postoperative Course

Morbidity.—A temperature of 100.4° F. was selected as representing the division between normal and febrile postoperative courses. On this basis, 11 per cent (281) of the patients were afebrile and 16 per cent (306) had fever for only one day. Fever persisted no more than three days in 55 per cent, no more than four days in 66 per cent, and no more than five days in 73 per cent. The greatest number suffered the highest fever on the second postoperative day. The highest temperature, irrespective of the day of occurrence, averaged 101.3° F. The average duration of the postoperative hospital stay was 12.7 days, although the limits ranged from seven to more than twenty days.

TABLE V. NATURE OF POSTOPERATIVE COMPLICATIONS

| | NUMBER OF PATIENTS |
|---|--------------------|
| Abdominal wound infection | 73 |
| Urinary tract infection | 59 |
| Shock necessitating treatment | 51 |
| Operative bed infection | 44 |
| Thrombophlebitis | 27 |
| Peritonitis | 23 |
| Superficial separation, abdominal wound | 23 |
| Hemorrhage, early | 17 |
| Dehiscence | 11 |
| Pneumonia | 11 |
| Miscellaneous* | 76 |

*Includes septicemia, pulmonary embolus, atelectasis, cardiac failure, late hemorrhage, foreign body, and urinary and bowel fistula.

TABLE VI. NATURE OF SECONDARY OPERATION NECESSITATED BY THE HYSTERECTOMY

| | NUMBER OF PATIENTS |
|---|--------------------|
| Wound closure (16 superficial, 11 dehiscence) | 27 |
| Drainage of abscess | 9 |
| Control of hemorrhage | 5 |
| Relief of bowel obstruction | 3 |
| Removal of foreign body | 1 |
| Repair of vesicovaginal fistula | 1 |
| Implantation of ureter into bladder | 1 |
| Miscellaneous | 6 |

In three instances two procedures were done on the same patient.

Nature of Postoperative Complications.—The principal postoperative complications are shown in Table V. Secondary operation was necessitated by the hysterectomy in fifty patients (2.5 per cent) and the required procedures are retailed in Table VI.

Fatalities.—Thirty-eight of the 1,925 patients died, a mortality rate of 1.97 per cent. The trend of the mortality rate is downward as shown in Fig. 7. During 1942, the rate was 0.51 per cent and during 1943 there was no death. In other words, there was only 1 death among the last 335 total hysterectomies. To illustrate the decreased mortality rate in another way, the series was arranged chronologically and divided equally. There were twenty-nine deaths in the first half and nine in the second half of the series, rates of 3.01 and 0.94 per cent, respectively.

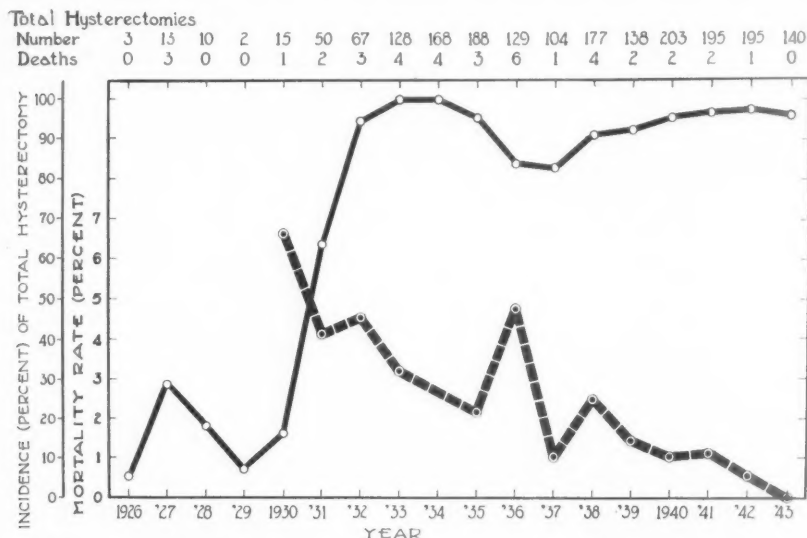


Fig. 7.—Annual incidence and mortality rates of total abdominal hysterectomy. Because of insufficient numbers, the mortality rates for the years 1926 to 1929 were not calculated. The gross mortality rate was 1.97 per cent, but twenty-nine deaths occurred during the first 877 (1926 to 1937, inclusive) hysterectomies and only nine in the last 1,048, rates of 3.08 and 1.05 per cent, respectively. Note that during 1942 and 1943 there was only one death from 335 hysterectomies, a rate of 0.3 per cent.

Postmortem examination was conducted on twenty-seven of the thirty-eight women.

The causes of death are grouped in Table VII. A more detailed study reveals that peritonitis was present in sixteen, pneumonia in six, and septicemia in four patients. Embolism accounted for six of the deaths, a fatality incidence of 0.3 per cent, or 1 in 321. Four of the fatalities occurred following fifty secondary operations, a mortality rate of 8.0 per cent.

TABLE VII. CAUSE OF DEATH

| | PATIENTS | |
|--------------------------|----------|----------|
| | NUMBER | PER CENT |
| Infection | 22 | 57.9 |
| Embolus | 6 | 15.8 |
| Exsanguination and shock | 3 | 7.9 |
| Cardiac failure | 2 | 5.3 |
| Other | 5 | 13.1 |

Comparison of Subtotal and Total Hysterectomy

Detailed comparison between the 393 subtotal and the 1,925 total hysterectomies reveals few essential differences. The subtotal mortality rate was 4.1 per cent, but since almost three-fourths of these operations were performed before 1932, the comparison is not valid.

Morbidity, postoperative complications, and causes of death were very similar in the two series.

The only significant difference lay in injuries to the urinary tract. The bladder was inadvertently opened eight times, 2.0 per cent, in the subtotal hysterectomies as against twelve times, 0.6 per cent, in total removal of the uterus. Bladder injury, therefore, is no more frequent in total hysterectomy and may be less because of the necessity for more adequate dissection.

Ureteral injury did not occur with subtotal but was incurred ten times with total hysterectomy, an incidence of 1 in 193 patients. Obviously a similar incidence with subtotal hysterectomy should have resulted in two such injuries.

Discussion

It is no part of the purpose of this paper to advocate the general adoption of elective total hysterectomy. Largely by circumstance, the Department of Obstetrics and Gynecology of the University of Iowa gave the elective performance of total hysterectomy a trial. The results were satisfying, and we believe we have demonstrated that total hysterectomy, performed mostly by young men in training, is a safe and reasonable operation. It was essential in the 12 per cent of the operations that were performed for malignant disease. If it be granted that removal of the cervix is desirable in the presence of pelvic inflammatory disease, then total hysterectomy was desirable in an additional 329 patients. In other words, removal of the cervix was essential or desirable in 563 patients, or 2 in 7. Any university department of obstetrics and gynecology actively engaged in training young men must, therefore, face the necessity of teaching the techniques of total hysterectomy. Since any technique improves with performance, and since this technique is a necessity for the gynecologic surgeon, it would seem that adequate training is desirable.

If elective total hysterectomy introduced a great hazard to the life, health, or happiness of the patient, such a position would be untenable. Since this is not the case, and since the results of this series can be duplicated in any acceptable institution, it would seem that our obstetric and gynecologic residents should be given the opportunity to acquire the technique of total hysterectomy.

Summary and Conclusions

1. Total abdominal hysterectomy was performed on 1,925 women, most of whom were white and indigent.
2. The majority of the patients (59.3 per cent) remained in the hospital from two to five days before operation. Only 12.4 per cent were operated on within twenty-four hours of admission.
3. The majority of the operations (63.4 per cent) were done by assistant residents or residents.
4. The principal indications for hysterectomy included fibromyoma, functional bleeding, pelvic inflammatory disease, benign and malignant ovarian and malignant uterine tumors.
5. Ureters were injured in ten women, with nine repairs, at the time of initial operation. Subsequent operation for reimplantation was necessary in one patient.
6. Morbidity rates were similar to those of any hysterectomy series, irrespective of the type of operation.

7. Fatality occurred in thirty-eight, or 1.97 per cent, of the patients. Twenty-nine (3.01 per cent) of the fatalities occurred in the first chronological half of the series and nine (0.94 per cent) in the second.

8. Infection of some type, chiefly peritonitis, accounted for twenty-two of the thirty-eight deaths.

9. Total hysterectomy in an indigent clientele can be performed without undue hazard by young men in training.

The drawings and the two charts were prepared by the Department of Medical Art, Southwestern Medical College.

Discussion

DR. A. D. CAMPBELL, MONTREAL, CAN.—In many instances the operation of abdominal hysterectomy is incidental to the proper surgical treatment of some extrauterine condition such as perforated diverticulitis involving the adnexa. Here the uterus must be removed in order to establish adequate drainage of the abscess. Similarly, carcinomatous growth of the ovary, filling the pelvis, threatens complete obstruction of the sigmoid. Colostomy may often be averted by removing this mass, in which case hysterectomy is part of the operation. Such factors are therefore bound to vitiate any statistical report on hysterectomies.

I have long been convinced that the cervix should not be divorced from the fundus of the uterus and that a supracervical hysterectomy should better be termed "incomplete hysterectomy."

Reviewing our experience at the Montreal General Hospital over a period comparable to that of Dr. Mengert's, that is from 1926 to 1943 inclusive, it is noted that incomplete hysterectomy was performed in some 76 per cent of cases during the first ten years, with a mortality rate of 2.64 per cent. Since 1934, in 1,800 consecutive hysterectomies incomplete hysterectomy was performed in 36 per cent of the cases, with an uncorrected mortality rate of 1.40 per cent, while in the last five years over 95 per cent of the hysterectomies done by us have been complete.

Except in very rare instances, there is no urgency for a hysterectomy. Since we have adopted the principle of more complete routine investigation, including blood sugar curve, urea, prothrombin time and electrocardiograph, our morbidity and mortality rate, as well as ultimate convalescence and early recovery, have been distinctly satisfactory. What might be termed a period of preoperative convalescence is given to each patient. During this time anemias are corrected and diet is supplemented by vitamins and essential mineral salts, while rest in preparation for operation is considered to be of paramount importance.

Prior to 1940 the morbidity following hysterectomy was higher in those with pelvic inflammatory disease when free pus was present in the peritoneal cavity. Most fatal of all gynecologic cases are those with secondarily infected hydrosalpinx. Since 1940 we have adopted the principle of marsupialization, whereby the peritoneal cavity is reconstructed. The infected, raw or deperitonealized area is thus placed extraperitoneally and allowed to drain through the unclosed vaginal vault. In none of the cases so treated have we had occasion to resort to the sulfonamides.

It is particularly worthy of note that in the four-year period, that is from 1940 to 1943 inclusive, in the Gynecological Clinic of the Montreal General Hospital only two patients died of peritonitis. Neither of these followed hysterectomy.

Postoperative complications are, to a considerable extent, in proportion to the operative technique. Minimal crushing of the peritoneum, a dry field, vaginal drainage, marsupialization of the deperitonealized pelvis, unnecessary exposure, silence in the operating room, as well as a carefully selected anesthetic, cannot be too strongly emphasized. Much, too, depends on the immediate postoperative care. In addition to posture, blood bank, plasma, etc., we have found that the amino acids, high in protein, in a 5 per cent glucose solution intravenously, expedite recovery, while diathermy (short wave) applied for the first few days postoperatively prevents distention. Adhering to these principles, the Levine tube is extremely rarely used.

The early recognition of impending complications must be emphasized. While frank thrombophlebitis is not particularly common, I feel that pulmonary emboli

with infarction of varying degrees very frequently occur without presenting the complete classical picture. The fatal pulmonary embolism is usually preceded by "warnings" if we could but interpret the symptoms. In suspected cases, an x-ray of the chest taken within three or four hours is of distinct diagnostic value. If such is not practicable, at least dicoumarin therapy in prophylactic doses should be immediately instituted. Since the physiologic response of dicoumarin is not obtained within forty-eight hours, heparin, which has an almost instantaneous effect, should be given over this induction period of forty-eight hours at the rate of 5 mg. in continuous intravenous saline infusion.

We have not had the same unfortunate experience as Dr. Mengert in damage to pelvic viscera: namely, the bowel, bladder, and ureters. Damage to the bladder should be a very rare accident unless its walls are deeply infiltrated by the existing morbid process.

At this point I should like to make a plea for the better training of our residents and junior attending staff in anatomy, as without a thorough practical knowledge of this subject one cannot hope to avert disaster. Accidents to pelvic viscera are, by and large, in exact proportion to the knowledge of practical and applied anatomy, which can be obtained only by a special training in the dissecting room.

DR. F. S. WETHERELL, SYRACUSE, N. Y.—I would like to discuss two phases of this paper: namely, deaths from infection and embolic deaths. I would like to ask Dr. Mengert how he prepares the vagina preoperatively? In some large clinics I have watched total abdominal hysterectomies performed with no gauze used in the preoperative preparation of the vagina. With a patient in Trendelenburg position, under spinal anesthesia, it is well to pack the vagina with gauze to prevent possible seepage of rectal contents into the vagina incident to relaxation of the anal sphincter.

Pulmonary embolism or pulmonary infarct, which usually occur within the first seven to ten days, are often not recognized by the gynecologist when the first symptoms begin to manifest themselves. He fails to realize the complete significance of a normal temperature or low-grade fever which suddenly changes and goes up a degree or more. At that time the patient herself will often complain of feeling uneasy and apprehensive. Those two little preliminary symptoms are important. He now fails to feel the calf muscles, to make pressure on the soles of the feet, and to do the Homan test of extending the feet on the legs. There is a time when it is perfectly proper to feel a woman's legs: namely, on the first day postoperatively. Thus the patient becomes accustomed to the amount of pressure made daily thereafter on the calf of the leg and on the sole of the foot; if there is a change toward tenderness, she will tell you.

An embolic death is a terrible thing and it can be avoided by careful routine examination. If tenderness and the other signs are present, there should be an immediate ligation of the femoral vein—not the institution of heparin or dicoumarin therapy. The thrombus as a rule starts in the veins of the soles of the feet and travels upward in the external saphenous which becomes the popliteal and then the femoral vein. The way to stop an embolus from getting into the lung or pulmonary artery is to tie off the vein. Even the common iliac vein can be tied with impunity. For that matter, the inferior vena cava has been tied. I would make a plea now that pelvic surgeons drop about an inch below the pelvis and learn how to do a ligation of the femoral vein because they may not have a general surgeon handy to do it.

DR. W. S. BAINBRIDGE, NEW YORK, N. Y.—I wonder if it would not have been of advantage to have made a thorough examination of the blood previous to operation in these cases? We examine for syphilis and some, like myself, also have the sugar content tested when the operation is not an emergency. As we frequently employ glucose after operation I believe that preoperative examination of the blood as to sugar content would be a move toward making the patient safer for the surgery. I noted also that among the cases reported there were a good many of excessive bleeding. A routine test for coagulation time, followed by proper medication if necessary, might have been of advantage.

In quite a number of the cases cyclopropane was employed. Certain of our large hospitals in New York refuse to permit any of it in the building as explosions and

a number of deaths have occurred from its use. What advantages does the author consider that it has over other anesthetics?

DR. MENGERT (closing).—Our patients were kept in the hospital from two to five or more days preoperatively and only a small number of them were operated upon within twenty-four hours. In general, they had careful and adequate preoperative preparation. Regarding Dr. Bainbridge's question, I think the coagulation time was generally omitted in these patients and it is likely that attention to this point may have prevented some of the bleeding. On the other hand, I think that a good deal of the bleeding might have been due to inexperience and the fact that these young men were learning.

In regard to Dr. Wetherell's question, we carefully prepared the vagina by scrubbing with green soap and water, painting with the antiseptic of choice which has varied through the years and, of course, the patient was catheterized. When the vagina was opened anteriorly a loosely fluffed sponge was immediately inserted to absorb any of the vaginal antiseptic that might be there. We have never made a practice of preparing the vagina in cesarean section. Quite a number of the cesarean hysterectomies were total hysterectomies and those patients get along perfectly well without any vaginal preparation. How important vaginal preparation is I do not know, but it was carried out routinely with the exception noted.

Our principal prophylaxis with regard to embolus has been to insist that the patient be turned from side to side and encouraged to move around freely. In recent years we have been getting patients up very early after operation. In general they have remained in bed nine or ten days, but a few of them have been treated with early activity and early rising from bed.

Cyclopropane alone certainly does not give adequate relaxation for pelvic surgery. At times patients returning from the operating room after that anesthesia have gone into shock, possibly attributable to the anesthetic. We have had no explosions and no suggestion of them although cyclopropane and ethylene have been in use at Iowa for a long time. The principal reason why cyclopropane has been used lately lies in the use of curare. The two seem to work very well together and the patient needs to be put into only a light anesthesia, barely rendered more than unconscious, and the musculature can be relaxed and the relaxation maintained for the duration of the operation.

END RESULTS IN THE TREATMENT OF CERVICITIS*

DAVID FINDLEY, M.D., OMAHA, NEB.

(From the Department of Obstetrics and Gynecology University of Nebraska,
College of Medicine)

IT WAS Carl Ruge of Berlin who, at the turn of the twentieth century, first demonstrated the pathology of cervicitis, and there followed a general understanding of the clinical significance of the lesion. But there remains to be developed a more uniform agreement on the choice of procedures to be applied in the management of the various phases of cervicitis. There is fairly universal acceptance of the therapeutic value of the cautery but there still is much confusion as to the type of cautery best suited for the individual case. With this in mind I have endeavored to determine for my own satisfaction the respective merits of the several methods of cauterization now in vogue, and to this end I have accumulated a series of observations on biopsies, both before and after cauterization, this to determine the method most favorable to complete healing and freedom from ensuing complications.

*Read by invitation at the Fifty-Sixth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 7, 8, and 9, 1944.

All types of cervical infections should be classified under the one heading—cervicitis. Subheadings, such as endocervicitis, erosion, cystic cervicitis, etc., merely designate the degree to which the pathologic process has advanced. Fundamentally the progression of tissue changes in all these conditions is quite similar—infection is followed by congestion with hypersecretion of the cervical glands, granulation tissue is infiltrated with polymorphonuclear leucocytes and bacteria. There is desquamation of the squamous cells covering the portio, and finally replacement by columnar epithelium.

Curtis¹ and Miller² both state that the columnar epithelium grows faster than the squamous type and is more resistant to chemical and bacterial irritants. It follows that irritation subsides and the more hardy and healthy squamous epithelium replaces the columnar cells, leaving scattered nabothian cysts and fibrous tissue.

Culbertson³ asserts that follicular erosions show an attempt at healing in which the ducts are occluded thereby giving rise to cystic formations. The presence of squamous cells on the surface suggests metaplasia, although Baer⁴ is of the opinion that these islets of squamous epithelium remain in the zone of the lesion and aid in rapid epithelization of the portio. Squamous cells in the gland lumen or stroma surrounding the glands suggest direct cellular proliferation and may be confused with carcinoma.

The sequelae of cervicitis are many and varied.⁵ There may simply be local manifestations, namely, leucorrhea, pruritis, frequency of urination, dysmenorrhea, and dyspareunia with possible resulting sterility. It may act as a focus of infection. Last, and of utmost importance, cervicitis is definitely a precancerous lesion. Phaneuf⁵ in 100 consecutive biopsies of well-advanced cervicitis found primary carcinoma in 10 per cent. J. Davis⁶ asserts that proper treatment would cause a 90 per cent reduction of cervical carcinoma. Although most authors cite a lower incidence of malignant change, it is generally accepted that carcinoma is a frequent sequel of cervicitis and that early irradiation of the lesion is the most effective prophylactic measure we possess. In this, I heartily concur.

A multitude of methods have been advanced for the treatment of cervicitis. Many have been discarded and some variations in technique have been introduced. At the present time the therapeutic procedures employed are topical chemical agents, autogenous vaccines, heat, cold, surgery, and electrosurgery. Novak⁷ states that caustics have some value in mild superficial infections but may cause stricture, while C. J. Miller⁸ and Black,⁹ among many, opine that topical chemical applications are of no value. However, as shown in Table II, I believe that beneficial results can be obtained by such chemicals where there is incomplete healing following other more drastic procedures. As for autogenous vaccines, they are, in my opinion, of questionable value in the treatment of cervicitis.

Heat therapy, in the form of diathermy, has among its advocates Corbus and O'Connor¹⁰ in the treatment of gonorrheal endocervicitis. The Elliot treatment has been advocated by Holden and Gurnee.¹¹ However, this procedure has few enthusiastic supporters.

Carbon dioxide snow has given some beneficial results according to Curtis¹ but its place is extremely limited.

Surgery in the form of trachelorrhaphy, tracheloplasty, and amputation has for years had many supporters. All, I think, will agree with Phaneuf,¹² Black,⁹ and Miller¹³ that trachelorrhaphy is at times indicated in women during the childbearing age and amputation or the Sturmdorf operation in the postmenopausal stage. Matthews¹⁴ is of the opinion that the Sturmdorf tracheloplasty does not interfere with labor

to a greater degree than trachelorrhaphy, and Mason¹⁵ believes, as do I, that the Sturmdorf operation is the best of all surgical procedures.

During recent years electrosurgery has almost completely replaced all other types of treatment for cervicitis. These procedures are grouped under three heads: actual or nasal tip cauterization, electrocoagulation, and conization. Each of these has a definite place in our therapeutic armamentarium and each has its advocates.

It is said that Hunner¹⁶ was the first to adopt the actual cautery with the accepted radial stroke technique. His best results were obtained in hypertrophy and erosion following childbirth. In his experience hemorrhage was frequently encountered. Moench and Schulman¹⁷ claim that the actual cautery is superior to all other methods in the treatment of nabothian cysts and prefers electrocoagulation in all other types of cervicitis. Goodall and Power¹⁸ obtained best results with electrocoagulation in superficial infections but point out the dangers of stenosis in deep carbonization. Baer⁴ reports fifteen years of office cauterization with only two late hemorrhages and one stricture. Matthews¹⁹ advocates the use of the actual cautery for recent and superficial infections but not for the more extensive lesions. Mason,¹⁵ in the use of the actual cautery, warns of fibrosis with contraction and the uncertain extent of tissue destruction. Masson and Powers²⁰ point out still another complication, namely, pelvic abscess. Cashman²¹ advises the passing of a sound at intervals for at least ten weeks following cauterization to forestall stenosis of the cervical canal. I personally feel that the nasal tip cautery is an excellent agent for the treatment of early postpartum erosions but not for the extensive long-standing cases because of the danger of hemorrhage and stenosis.

Electrocoagulation has gained many advocates in the past few years. Frost²² finds that healing takes place with a minimum of scar tissue except when used with high voltage. He asserts that healing occurs in about four weeks but warns that the method should not be employed in the presence of pelvic inflammation. Black⁹ is of the opinion that electrocoagulation is more apt to be followed by infection than is either cauterization or conization, listing hemorrhage, stenosis, atresia, cellulitis, pelvic abscess and peritonitis as occasional complications. He wisely points out that penetration of the uterine cavity increases the danger of infection. Maryan²³ and Moench and Schulman¹⁷ list the advantages of electrocoagulation over other methods. These include: (1) a controllable, uniform penetration with minimum carbonization; (2) more rapid destruction of diseased areas; (3) no accidental injury because the current is easily controllable; (4) less scar tissue formation. The above is an impressive array of advocates of electrocoagulation, but it is to be observed that though electrocoagulation is in universal practice there is a wide discrepancy in many of the details both in technique and in indications.

Hyams²⁴ was one of the first to adopt conization in the treatment of cervicitis. He claims the beneficial results were due to the removal of the diseased glands, that the danger of hemorrhage was almost nil, and that resultant scar tissue was minimal. This, in my experience, is refuted by Table V and also by numerous cases not included in my report. Boland²⁵ reports that conization produces a thin layer of coagulation and desiccation which does not interfere with primary healing but does tend to prevent bleeding and infection by sealing over the blood and lymph channels. In his cases healing occurred in four to eight weeks. Stadium²⁶ would perform conization in hypertrophy and elongation of the cervix and says that though there were frequent hemorrhages subsequent labors were not interfered with. Royston²⁷ reports that hemorrhage was present in 1½ per cent of 275 cases and that scar tissue formation was greater than that following electrocoagulation. N. F. Miller²⁸ observed stenosis in from 6 to 10 per cent of cases following conization. Novak⁷ states that, in general, conization is less favor-

able than other methods in the treatment of cervicitis. Here again we find the authorities quoted above fall short of agreement on many details. For my own part, I have abandoned conization for fear of hemorrhage, which in my hands has occurred to an alarming degree as late as the third week following operation.

Personal Observations

My series includes 240 cases of chronic cervicitis, with or without erosion, cysts, eversion, or hypertrophy. No immediate postpartum lesions are included. I have endeavored to determine the degree of healing in the various groups. These groups include the cases treated by the accepted methods of cauterization, to wit, nasal tip, coagulation, and conization. The number of treatments are recorded, the degree of sloughing is noted, as are the complications following the application of the cautery.

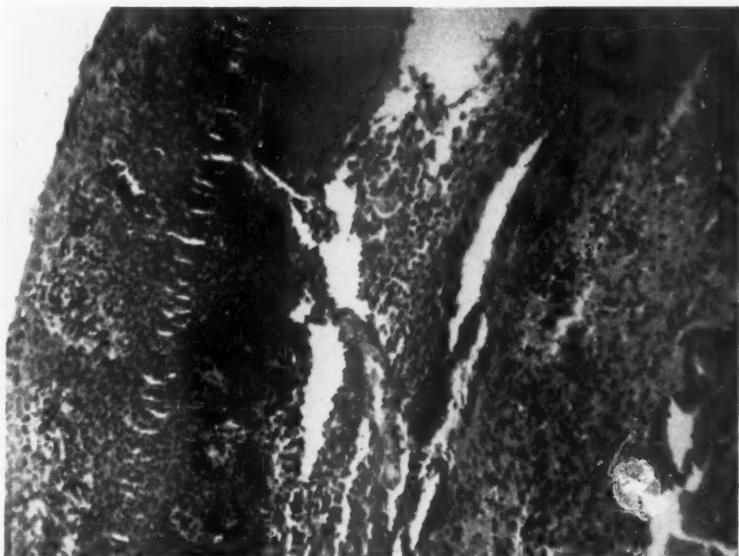


Fig. 1.—Mrs. G. M. Biopsy Sept. 4, 1941. Chronic cervicitis with erosions showing dense submucous leucocytic infiltration and desquamation of squamous epithelium. Treated by nasal tip cautery.

Table I includes the total number of cases with varying degrees of erosion and the type of treatment employed.

TABLE I. TOTAL CASES—240

| DEGREE OF EROSION | NASAL TIP | COAGULATION | CONIZATION |
|-------------------|-----------|-------------|------------|
| None | 22 | 24 | 20 |
| First degree | 28 | 24 | 4 |
| Second degree | 32 | 30 | 21 |
| Third degree | 15 | 8 | 12 |
| Total | 97 | 86 | 57 |

All nasal tip cauterizations were done in the office and were superficially done because of lack of anesthesia. Those treated by electrocoagulation and conization were hospitalized and a more thorough treatment was carried out under general anesthesia.

Table II reveals the number of patients requiring one or more treatments before satisfactory results were obtained. As noted, several cases were treated with topical applications as well as by electrosurgery.

TABLE II. NUMBER OF PATIENTS

| NUMBER OF TREATMENTS | NASAL TIP | COAGULATION | CONIZATION |
|------------------------|-----------|-------------|------------|
| 1 | 56 | 52 | 57 |
| 2 | 22 | 15 | 0 |
| 3 | 4 | 10 | 0 |
| 4 | 6 | 1 | 0 |
| AgNO ₃ -25% | 9 | 8 | 0 |
| Total | 97 | 86 | 57 |

This report differs from others published advocating electrocoagulation. Fine²⁹ states that in his series 39 per cent required but one treatment, 61 per cent, two or more. Baumrucker and Baumrucker³⁰ claim that 82 per cent were healed after one coagulation. In my series 52 required but a single treatment; 34 required two or more treatments.

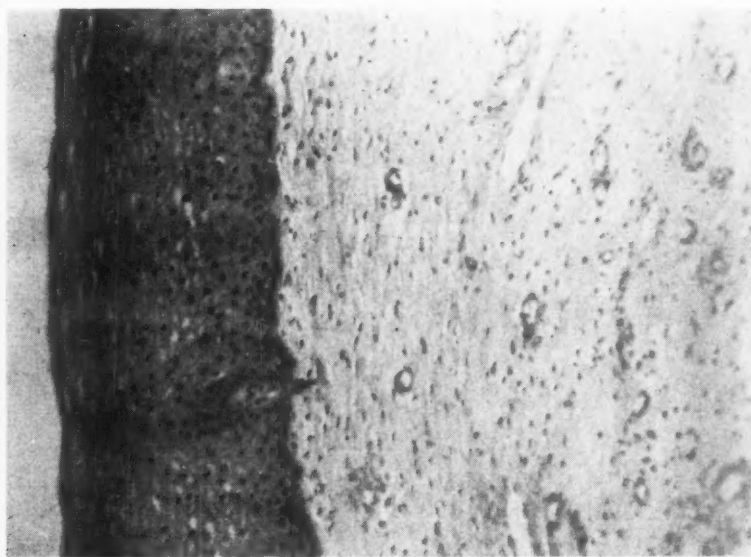


Fig. 2.—Mrs. G. M. Biopsy of anterior lip Nov. 6, 1941, showing complete healing with minimal fibrosis and obliteration of blood vessels.

An attempt was made by close follow-up to determine the reactions of cervical tissue to these various methods of treatment. As far as possible cases were observed at weekly intervals. However, as many of the patients seen came from scattered sections of the state, subsequent checkups were made through the cooperation of the local physicians. Unfortunately, because of war priorities, equipment was not available to photograph the cervix during these stages in order to show the gross changes taking place during the early weeks following treatment. For a characteristic photographic record the reader is referred to the article previously mentioned.³⁰

It is noted in Table III that there is a very little difference in elapsed time among the three classifications as to when the slough is at its height, when it is completely separated and granulation and epithelization begin, and when healing is clinically complete.

These figures vary markedly from those of Jacoby³¹ who found clinical cures from the cautery in four months, coagulation in seven months, and conization in 7.3 months. Baumrucker and Baumrucker³⁰ claim

TABLE III

| HEALING | NASAL TIP | COAGULATION | CONIZATION |
|------------------|-----------|-------------|------------|
| Slough at height | 7 days | 9 days | 9 days |
| Slough separated | 17 days | 19 days | 15 days |
| Healing complete | 7½ weeks | 7½ weeks | 7+ weeks |

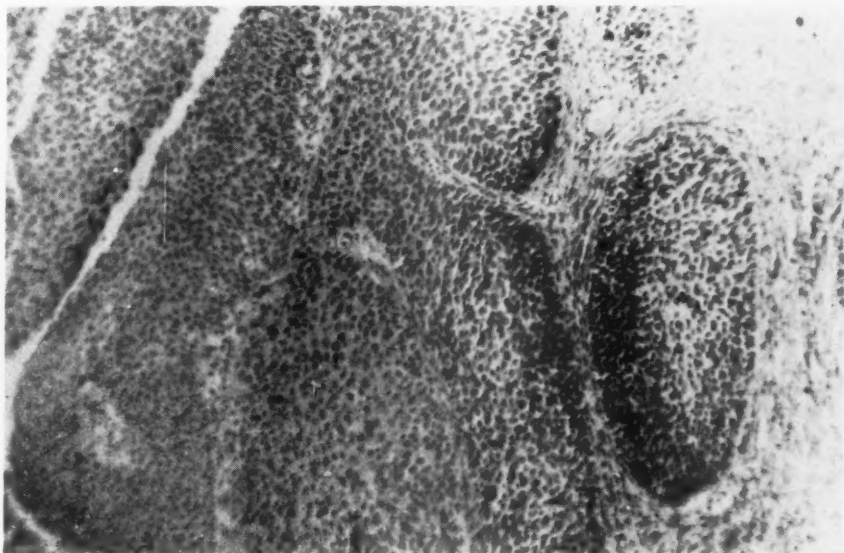


Fig. 3.—Mrs. G. M. Biopsy of posterior lip Nov. 6, 1941, showing a Grade II squamous cell carcinoma overlooked in previous biopsy.

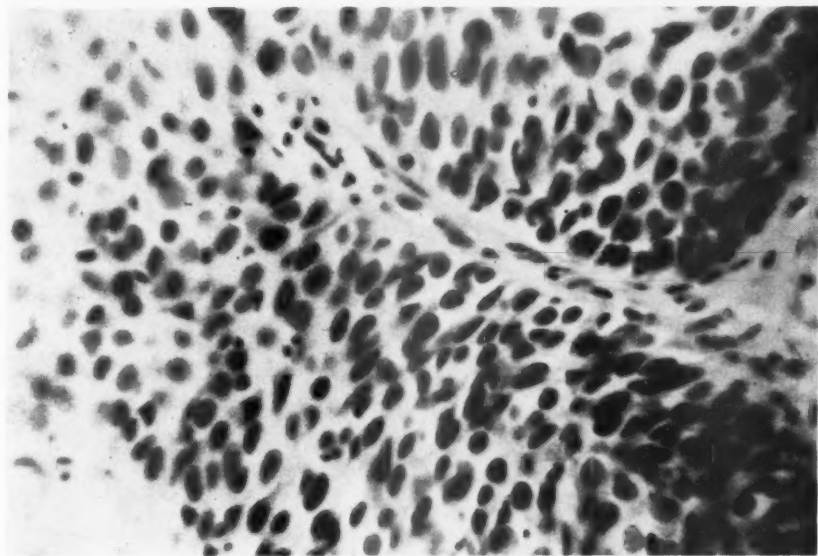


Fig. 4.—Mrs. G. M. High magnification of Fig. 3.

healing occurred in ten weeks or less in 75 per cent of cases following coagulation. Barrett³² reports healing in from four to six weeks and Kimble³³ in six to eight weeks.

It is apparent that the large percentage of subsequent endocervicitis and erosion following treatment, as seen in Table IV, resulted because the electrosurgical procedure was not carried high enough in the cervical

canal to reach and destroy all of the infected cervical glands. There was little excuse for this in the series done by electrocoagulation and conization because these patients were under surgical anesthesia. All cases treated by the nasal tip method were handled in the office without anesthesia so that a thorough and complete procedure was seldom carried out.

In Table IV we observe the percentage of cures and less favorable end results. Under the term "endocervicitis" are included all cases seen with a subsequent excessive mucoid or mucopurulent discharge.

TABLE IV. END RESULTS

| RESULTS | NASAL TIP (%) | COAGULATION (%) | CONIZATION (%) |
|----------------|------------------|--------------------|-------------------|
| Healing | 50 | 78 | 72 |
| Erosion | 24 | 9 | 3 |
| Endocervicitis | 24 | 12 | 25 |
| Failure | 2 | 1 | 0 |

TABLE V. COMPLICATIONS

| COMPLICATIONS | NASAL TIP | COAGULATION | CONIZATION | TOTALS |
|---------------|-----------|-------------|------------|--------|
| Carcinoma | 1 | 0 | 1 | 2 |
| Hemorrhage | 0 | 2 | 4 | 6 |
| Stenosis | 0 | 1 | 4 | 5 |
| Pyometra | 0 | 1 | 1 | 2 |
| Infection | 0 | 0 | 0 | 0 |

Most authors agree that certain complications are bound to result no matter what type of treatment is employed. The complications most often observed are hemorrhage, stenosis, pyometra, and pelvic inflammatory reaction. A few essayists stress the importance of suspecting carcinoma in cases which do not respond to local treatment. Table V reveals the complications noted in my limited series. Both of the cases of carcinoma were recognized only by microscopic examination of routine biopsied tissue. Neither was suspicious macroscopically. One of these patients was biopsied on first observation and reported as purely a benign inflammatory process. Upon repeated treatments, however, the lesion failed to heal, and subsequent biopsy revealed a low-grade squamous cell carcinoma.

Hemorrhage occurred in six of the 240 cases. In two of these, both following conization, the amount of bleeding was alarming, and one required transfusion to replace the blood loss. I have seen several other cases not included in this report that had had repeated profuse hemorrhages following conization. One required thirteen transfusions and three attempts at suturing the cervical branch of the uterine artery before recovery occurred. Karnaky³⁴ reports 1 per cent hemorrhage following electrocoagulation, 3 per cent after cauterization and conization alike.

Stenosis of the cervical canal occurred most frequently following conization. The principal reason for this is that many of these cases were not under my control, and periodic dilation of the cervix was not done by the patient's local physician.

Presented in this series were several obstinate cases which, after repeated cauterization, revealed no beneficial results. On questioning these

patients it was found that they were using internal menstrual tampons. Repeated cauterization and a change in the type of protection resulted in prompt healing. The results are noted in Table VI.

Karnaky³⁴ reports end results in the treatment of cervicitis. He claims conization is superior to other methods, that it gives but a 1 plus or 2 plus fibrous tissue reaction and obliteration of blood vessels. Coagulation was followed by a 2 plus fibrosis and cautery by a 4 plus reaction. In my study of cases reported, the above figures were varied. A low fibrous tissue reaction following nasal tip cautery was found because all cases were treated lightly. There was little difference between coagulation and conization in the end histological pictures. These reactions were slightly more pronounced than after nasal tip cauterization.

Conclusions

1. Two hundred and forty cases of chronic cervicitis were treated by the three generally accepted methods of electrosurgery, namely, nasal tip cauterization, electrocoagulation, and conization.
2. Histological studies were made before treatment and after healing was clinically complete.
3. Comparisons were made as to the rate and type of healing following each therapeutic measure and also as to resultant complications.
4. The average rates of healing were found to be the same with all three methods.
5. The percentage of satisfactory results was greatest after electrocoagulation, second after conization, and least following cauterization.
6. There was very little difference between coagulation and conization in the end histological picture. Fibrous tissue reaction was very low in both procedures although slightly greater following cauterization.
7. Complications most commonly encountered were hemorrhage, stenosis, and pyometra, and were most frequently seen following conization.
8. Hemorrhage usually occurs from the tenth to the fifteenth day at the time of separation of the slough.
9. Stenosis with resultant pyometra may be largely prevented by repeated dilation of the cervical canal.
10. Carcinoma was discovered in two unsuspected cases out of 240 examined.
11. Internal menstrual tampons were found to interfere with proper healing. Their use is to be condemned.

I wish to express my appreciation to Mrs. Glenn Streby for her cooperation in the preparation of the microscopic slides and to Dr. Charles Baker for his help in preparation of the photomicrographs.

446 AQUILA COURT BUILDING

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Discussion

DR. WALTER T. DANNREUTHER, New York, N. Y.—No single therapeutic method is applicable to all cases of infection and damage resulting from birth trauma indiscriminately. Where there has been a recent transverse laceration with simple ectropion, without infection, stripping of the eroded areas with a fine wire cautery tip, repeated two or three times at three-week intervals, will result in retraction and contraction and satisfactory healing. For cases of deep-lying infections in the compound racemose glands of the endocervix, conization will completely remove the diseased tissue with no damage to the rest of the portio, provided a very high tension current which is free from any desiccating effect and the original Hyams electrode are used, and the technique described by Hyams is followed exactly. Under such circumstances, hemorrhage, stenosis, or pyometra should never occur. For the multiparous woman with an extensively scarred, cystic, and infected cervix, extirpation is the safest method of treatment, and personally I prefer hysterectomy, either vaginal or abdominal, to amputation. The greatest disadvantage of electrocoagulation is the operator's inability to control the depth of heat penetration and consequent destruction of tissue, and in my experience it has been the most common cause of cervical stenosis, dystocia at the time of labor, and secondary hemorrhage. The sole virtue of silver nitrate applications lies in their ability to stimulate the proliferation of squamous epithelium.

I believe that Dickinson and not Hunner should be credited with originating cauterization for the treatment of endocervicitis.

Perhaps the differences in the viewpoint of Dr. Findley and myself can be explained by technical variations in his hands and mine.

DR. MELVIN A. ROBLEE, St. Louis, Mo.—For the past fourteen years in the Washington University School of Medicine Outpatient Department in St. Louis we have had all cases of cervicitis referred for therapy to the cervicitis clinic. The assistant resident, under close personal supervision, has had this as his clinic for a six-month period. Each year a few cases of chronic cystic cervicitis are cauterized with nasal tip cautery by the intern who will become the assistant resident. He again sees these patients six months to one year later in order to demonstrate the temporary nature of noted improvement.

Our assistant residents are instructed to use a conization electrode only one time within the cervical canal, never to recut except to undermine the cervical lips of the external portion of the cervix with another electrode which locates the cutting element in the proximal portion only. The distal part in contact with the internal

os contains no cutting element. An ordinary biopsy loop could be used to undercut the external portion of the cervix which contains nabothian cysts.

For the past two years we have directed attention to the local application of sulfonamides to the coned cervix at the time of operation and as postoperative care. Healing time is much faster. Complicating secondary hemorrhage and stenosis have been reduced. Unless great care is exercised not to damage the internal os of the cervix, conization will be limited to women past the childbearing age. On the other hand, if deep cutting is limited only to the nabothian cystic areas of the external portion of the cervix, and if sulfonamides are used locally postoperatively, good clinical results have been our experience.

DR. FINDLEY (closing).—I agree with Dr. Dannreuther that great care should be taken in the application of any and all procedures involved in the cauterization of tissues. To this end we have on numerous occasions applied the cautery to raw meat to demonstrate the extent of its penetration. We are mindful of the fact that excessive carbonization may lead to stenosis and hemorrhage.

I have followed Dr. Roblee's technique of applying sulfonamides in buffered acid jelly to the cauterized cervix on a number of patients with gratifying results, although there were not a sufficient number of cases to be included in this paper.

SEX PRECOCITY, VIRILISM, ADRENAL CORTICAL TUMOR*

J. P. PRATT, M.D., AND ROBERT L. SCHAEFER, M.D., DETROIT, MICH.

(From the Henry Ford Hospital)

SEX precocity assumes practical importance as a physical and psychologic problem. By comparison of the three cases presented here, two of the patients are quite obviously precocious while the third is only border line. Although certain standards are accepted as normal, one must permit considerable variation in both time and degree of development. The life of an individual consists of a series of transitions from one phase to another. The neutral segmenting ovum soon develops to a stage at which the gonads indicate the male or female future. At birth, all of the sex characters are present, though some of them are rudimentary. Through childhood, puberty, and adolescence, the development continues to maturity. Disturbance of development during childhood may result in sex precocity.

Sex differentiation is complex. Though one believes that genes determine whether the gonad will be male or female and that the gonads primarily control the determination of the sex characters, the secondary factors that control the function of the gonads are not so readily correlated.

Classification of sex precocity is difficult because no two cases reported are exactly alike. The alteration in development may be due to (1) endocrine hyperfunctional tumors (adrenal, ovary, testis), (2) endocrine hyperfunction with or without cellular hyperplasia, (3) tumors in the region of the third ventricle, and (4) pineal tumor.

Sex precocity is not rare, nor can it be considered uncommon. In a former study by one of us (R. L. S.) a survey of 2,311 delinquents

*Read at the Fifty-Sixth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 7, 8, and 9, 1944.

in the preadolescent and adolescent age groups revealed that sex precocity occurred in thirteen, or 6.8 per cent, of the patients. It is desirable that many cases be reported for comparison. Three cases are presented here.

CASE 1.—T. P. was referred by Dr. G. A. Domzalski. She was 2 years, 9 months old when seen April 3, 1937. The diagnosis was virilism and adrenal cortical tumor. One month before the first visit to the doctor, the mother had noticed an unnatural swelling of the genitals. It was assumed that the child had been injured by a fall a few days previously. The development of the child had been normal except for recent rapid growth, change in the genitals, and development of pubic hair. Family history and past history were essentially negative. The child had measles and chicken pox at 8 months without complications.

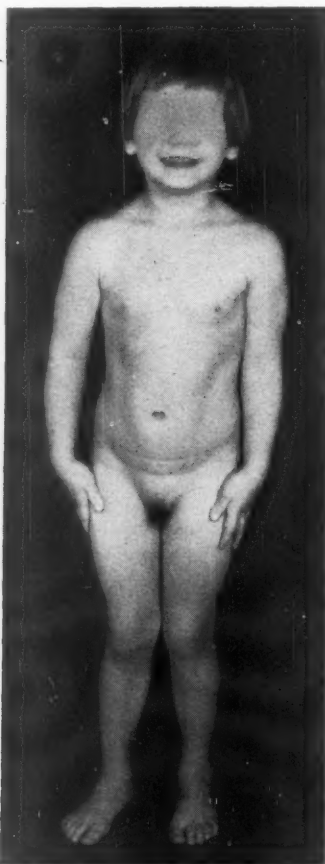


Fig. 1.



Fig. 2.

Fig. 1.—Case 1. Taken at the age of 2 years, 9 months. Shows masculine trend and precocious development.

Fig. 2.—Case 1. Taken at the age of 2 years, 9 months. Shows the large labia minora, clitoris, and coarse pubic hair.

Physical examination: The child appeared large for her age. Her actions were more mature than expected. The muscular development was masculine (Fig. 1). The nose was large and bulbous. The deep voice was startling. The color of the hair was light, the texture fine, and the distribution scant. The pubic hair was coarse, stiff, and black. The enlarged clitoris protruded between the relatively large labia minora (Fig. 2). A small bluish tip on the end of the clitoris suggested a glans. The labia majora were enlarged. The vagina and vestibule were congested and secreted a mucoid substance.

| | ACTUAL | NORMAL VARIATIONS |
|-------------------|-------------|-------------------|
| Weight | 36.0 pounds | 24.7-30.7 pounds |
| Height | 39.0 inches | 33.9-36.3 inches |
| Span | 40.0 inches | 32.4-34.8 inches |
| Upper measurement | 22.0 inches | 19.6-21.0 inches |
| Lower measurement | 17.0 inches | 14.0-15.4 inches |

Laboratory procedures: The following laboratory tests were done and all were found to be entirely within normal limits: urinalysis, blood count, blood sugar, blood nonprotein nitrogen, blood calcium, blood phosphorus, blood cholesterol, Kahn, basal metabolism. Roentgenogram of the skull revealed a normal sella turcica. Osseous development was studied by roentgenogram of the following joint regions: shoulder, elbow, wrist, hip, and ankle. An advance in osseous development of three years was evidenced. A flat plate of the abdomen was negative. Bio-assay of the urine on two separate occasions, reported by Dr. Oliver Kamm, was negative for estrogens and androgens.

During six months of observation the patient increased six inches in height and gained twelve pounds due to continued muscular development. The voice was deeper, the pubic hair increased slightly, and the external genitals were more conspicuous. A few coarse hairs appeared around the nipples. Hair began to develop in the axilla.



Fig. 3.—Case 1. Adrenal cortical tumor which measured 5.5 by 4.5 by 3.3 cm.

Operation, Jan. 15, 1938: The abdomen was opened by right rectus incision. Exploration of the pelvis showed the uterus to be about the size of the distal joint of the thumb. The ovaries and tubes appeared normal for a child of the patient's age. The surface of the ovaries was smooth. A few follicles, showing beneath the surface, were apparently normal. The left suprarenal gland appeared normal. In the right suprarenal gland a circumscribed nodule occupied the space of the gland and was fixed to the kidney. The well-encapsulated mass was completely removed through an incision in the peritoneum in the right renal region. The vessels around the periphery of the mass were ligated without difficulty.

Pathologic report by Dr. C. A. Payne.—Grossly the specimen consisted of an adrenal gland (Fig. 3). The adrenal weighed 48 Gm. and

measured 5.5 by 4.5 by 3.3 cm. The gland was surrounded by loosely arranged connective tissue. The capsule was quite vascular. The gland contained an egg-shaped nodule which obliterated the normal contour and left only a thin rim of recognizable tissue. The tumor cut with moderate ease and presented a slightly bulging red-gray surface with many small, irregular, orange and yellow plaques distributed throughout the periphery. The tumor was fairly soft, apparently cellular, and quite vascular. Only small remnants of adrenal tissue were identified.



Fig. 4.

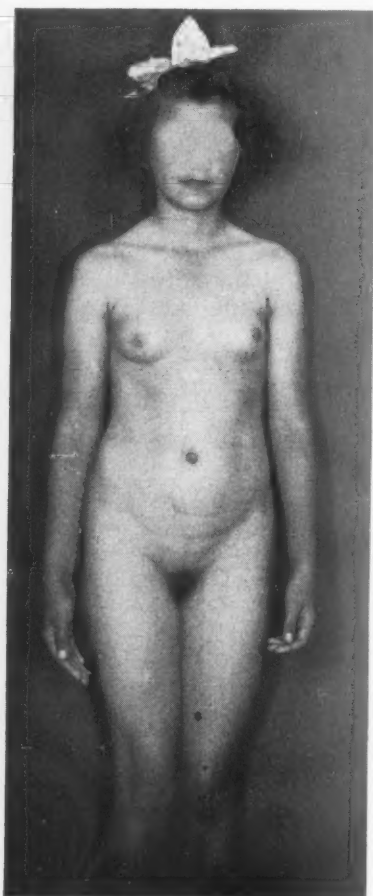


Fig. 5.

Fig. 4.—Case 1. One year after removal of tumor. Masculine trend diminishing.

Fig. 5.—Case 1. Taken at the age of 10 years. Shows feminine development in breasts and general contour of the body. Pubic hair only slightly increased.

Section through the tumor showed, in many areas, a rather definite fibrous capsule outside of which compressed and atrophic strands of cortical cells showing hemorrhagic infiltration were noted. The entire tumor was rather uniform in structure and was not unlike that seen in the normal adrenal cortex. The cells were of uniform size and shape and showed vesicular nuclei with varying degrees of chromatin and small nucleoli. The cells varied in size and shape but nothing suggested malignant degeneration. No mitotic figures were seen in the sections examined. The cells were arranged in strands and cords, and, in many areas, in definite adenomatous structures. Numerous sinusoids, many of which were filled with blood, were noted in the sections examined. Small areas of calcification and other areas of fibrosis were noted throughout the very scant stroma. Only small groups of the tumor cells pre-

sented a foamy or vacuolated cytoplasm similar to those noted in the normal adrenal cortex. The other cells had a rather deep staining eosinophilic cytoplasm which was slightly granular. Impression: Cortical adrenal carcinoma.

The postoperative course has been uneventful. Observations at intervals during six years have indicated no suggestion of metastases. The configuration of the body has been transformed to a more feminine type due to the relative increase of adipose tissue over muscular development (Figs. 4 and 5). Although the voice is still deep, it is less conspicuous than at the time of the operation, as has been determined by comparison of vocal recordings. The child's behavior is now characteristic of a girl of her age. The pubic hair remains unchanged. The labia and clitoris have diminished in size. The mucoid discharge has disappeared. There has been no progress in the growth of hair in the axillary or mammary region. The growth rate has returned to normal. Her measurements three years after the operation were as follows:

| | ACTUAL | NORMAL VARIATIONS |
|-------------------|-------------|-------------------|
| Weight | 58.0 pounds | 39.2-48.8 pounds |
| Height | 51.0 inches | 44.2-47.2 inches |
| Span | 51.0 inches | 42.8-46.0 inches |
| Upper measurement | 25.5 inches | 23.0-25.0 inches |
| Lower measurement | 25.5 inches | 20.5-22.5 inches |

Summary.—A girl, aged 2 years, 9 months, who showed marked signs of virilism, was operated upon and an encapsulated tumor in the right adrenal was removed. At the end of a period of six years there have been no signs of metastasis. There has been a marked reversal from the original picture to that of the normal female child.

CASE 2.—D. B., a female, aged 4 months when first seen, was born in April, 1935, and died May 15, 1937. She weighed 7 pounds at birth. Her physical and mental development was normal. She had fits of temper. Her appetite was excessive. At the age of 4 months a small tumor appeared on the left cheek close to the angle of the mouth. Thinking it was a blackhead, the parents squeezed it but obtained no secretion. A physician lanced the lesion but obtained only blood. The lump appeared at the age of 13 months as an ulcerated, fungating mass, 4 cm. in diameter. Biopsy taken May 19, 1936, was reported as follows: Gross examination: The specimen was a small piece of tissue 0.5 cm. in diameter. Microscopic examination: The specimen was a newly grown tissue with a slight fibrillary stroma. It was composed of cells which were highly anaplastic varying considerably in size, shape, and staining. In general they were spindle-shaped with some tendency to polygonal morphology. Many of them contained mitotic figures and a number of large multinucleated cells were present.

Following biopsy and x-ray therapy, the tumor receded, disappearing within four months. An indurated scar remained. Hair distribution increased, including heavy black hair on the head, a beard, and black pubic hair of the masculine type. The size and facial expression indicated an older child. The ears and nose were large. She had heavy bones and a large chest. Her voice seemed deep and husky. The clitoris and labia were overdeveloped. Hyperemia of the genitals was noted.

Laboratory procedures: Roentgenogram of the skull at the age of 15 months revealed a normal sella turcica. Roentgenogram of the chest showed a shadow, approximately 7 by 10 mm., in the region of the left hilus, suggesting a small gland. Osseous development in the elbows, knees, and pelvis was advanced from two to four years. A plain film of the abdomen gave no evidence of renal tumor. A Friedman test was negative. Fifteen hundred rat units of theelin per twenty-four hours were found in the urine.

In December, 1936 (age, 20 months), there was a recurrence of the lesion on the face. The hair development had increased. The voice was

even deeper. The larynx was prominent. The enlarged clitoris now suggested a phallus with hypospadias.

Roentgenogram of the abdomen showed a soft tissue mass the size of a fist in the left upper abdomen. It did not appear to be a spleen but suggested a lobe of the liver or an adrenal tumor.

Laparotomy Dec. 15, 1936, by Dr. A. J. Font: A right paramedian incision was made from 1.5 inches below the umbilicus to the symphysis pubis, and the peritoneal cavity was entered. The pelvic organs were explored and were found to be normal. On exploration the right kidney was found to be normal. Exploration of the left kidney revealed a palpable mass the size of a lemon in the region of the kidney. Due to the location of the incision, no further exploration was done and the abdomen was closed.

Laboratory tests following operation showed a normal nonprotein nitrogen, blood chlorides, blood sugar, blood calcium, blood phosphorus, blood count, and urinalysis.

Cystoscopic examination Jan. 7, 1937, by Dr. G. C. Burr: Inspection of the external genitals revealed a precocious development, particularly of the clitoris, which was greatly hypertrophied. As a result of this hypertrophy the urethra had the appearance of a hypospadias in the male. However, the urethra itself was normal and admitted a No. 16 French scope. The urine was clear and the bladder was normal throughout. The right and left ureteral orifices were normally placed and functioning. The urine from each kidney was clear. A pyelogram was made of the right side and then on the left side. Inspection of the roentgenogram revealed a normal kidney on the right side. The calyces were stretched out in the upper portion of the left kidney, suggesting involvement of that portion of the kidney in the tumor mass. This, however, was not marked and the kidney might well be normal in its entirety. Diagnosis: Precocious sexual development and adrenal tumor.

After the laparotomy, pus drained from the wound for four weeks. Temperature reached 104° F. In late January and early February, 1937, deep x-ray therapy was applied over the tumor of the cheek with no apparent effect. In April the patient complained of severe pain in her hip. The lesion on the face had enlarged. Metastases had appeared in the left lung, the cheek, and the bones. She failed rapidly and died May 15, 1937, at the age of 25 months.

Microscopic examination of the tumor obtained at autopsy: The tumor tissue of the left adrenal, lungs, pleura, cranium, and neck was found to be of the same structure. Likewise, it was found to be identical with the biopsy of the lip lesion which was made a year previously. The tumor tissue was composed of a variety of cells which varied greatly in size, shape, and staining. Most of them were large and contained large nuclei. The staining of the nuclei varied greatly, some of them being hyperchromatic and others staining poorly. Some of the cells were multinucleated. The cytoplasm was abundant, nongranular, and stained poorly. The cell borders were indistinct. There was no differentiation into glands and no adrenal zones were being produced. The stroma was scanty and fibrillary. Microscopic examination of the metastatic processes showed a similar picture. The anterior lobe of the pituitary gland contained an abundance of alpha or acidophil cells. The liver and spleen exhibited a moderate engorgement of the vascular system, otherwise no pathology. The ovaries exhibited a large number of follicles; some were immature and some were nearly mature. There were a number of poorly formed corpora albicantes. Section made through the base of the clitoris revealed large corpora cavernosa.

Summary.—A female child at 4 months of age presented signs of virilism which increased until near her death at the age of 25 months. The first lesion noted was fibrosarcoma of the cheek. This metastasized to the left adrenal which accounted for the signs of virilism. The death of the patient was due to the malignant tumor of the cheek and its

metastases. The virilism appeared as a consequence of metastases to the adrenal.

CASE 3.—D. B., a female, showed virilism and retarded growth. Her age was 8 years, 4 months Nov. 19, 1938.

Developmental history: The patient's birth weight was 6 pounds, 2 ounces. The mother's endocrine response to the pregnancy was normal. Other developmental advances, such as walking, talking, and teething, were entirely normal. There were no complaints until the age of 5 years, at which time failure to grow was noted. There had been a growth of only two inches in the previous two years. At the age of 7 years, pubic hair was first noted, and since that time an increase in length and number had been evident. Increased growth of hair on the arms and legs was noted. The child was precocious and in an advanced group at school. The parents revealed that excessive strength had always been present. She had always been "tomboyish," being an excellent trapeze performer. Both the family and past history were essentially negative.

Physical examination:

| | ACTUAL | NORMAL VARIATIONS |
|-------------------|-------------|-------------------|
| Weight | 48.0 pounds | 48.6-60.6 pounds |
| Height | 43.5 inches | 48.2-51.6 inches |
| Span | 45.0 inches | 47.5-51.1 inches |
| Upper measurement | 23.5 inches | 24.4-26.6 inches |
| Lower measurement | 20.0 inches | 23.4-25.6 inches |

The child was moderately well nourished. Musculature was excessively developed and of the male type. This was especially true of the muscles of the upper legs. An excessive hair growth was noted on the arms, legs, and lumbosacral region. There were approximately thirty or forty black pubic hairs on each side, measuring one inch in length. There were no signs of voice change, axillary hair, or breast development. The labia were enlarged. The clitoris was well formed.

Laboratory procedures: The following laboratory tests were done and all were found to be entirely within normal limits: urinalysis, complete blood count, blood sugar, blood nonprotein nitrogen, blood calcium, blood phosphorus, Kahn, basal metabolism. Blood cholesterol was increased, being 241 mg. per 100 c.c. of blood. This test was repeated after two days and the amount was 230 mg. per 100 c.c. of blood. Bio-assay of the urine was negative for estrogens and androgens.

Roentgenogram of the skull revealed a normal sella turcica. Roentgenogram of the chest for thymus was normal. X-ray of the abdomen revealed no abnormal shadows in the adrenal area. Roentgenogram, following air injection in the adrenal area, did not reveal signs of abnormal shadows. X-ray study for osseous development revealed an advance of one to two years.

Course: On Jan. 5, 1939, at the age of 8 years, 6 months, an exploratory operation was done. The uterus was found to be small for a child of the patient's age. The tubes were normally developed. The ovaries appeared to be normal, about 0.20 cm. in length. The surface was smooth. Five or six pink follicles showed through the surface, but there were no visible corpora lutea. There was no enlargement of the adrenals. No physical findings at the exploratory operation explained the sex precocity.

The patient was last seen Aug. 7, 1940, at the age of 10 years, 1 month, and the following measurements were recorded at that time.

| | ACTUAL | NORMAL VARIATIONS |
|-------------------|-------------|-----------------------|
| Weight | 60.0 pounds | 56.2-71.0 pounds |
| Height | 47.0 inches | 51.2-54.8 inches |
| Span | 48.0 inches | 50.7-54.5 inches |
| Upper measurement | 25.0 inches | 25.5-27.9 inches |
| Lower measurement | 22.0 inches | 25.1-27.5 inches |
| Chest | 24.0 inches | 25.0 inches (optimal) |
| Abdomen | 22.0 inches | 21.8 inches (optimal) |

Examination revealed that there had been a slight but definite increase in pubic hair. The breasts still showed no signs of development. An occasional axillary hair was noted. The musculature and build were still of the masculine type.

The mother reported that the masculine tendencies decreased and the femininity increased.

Summary.—This girl, aged 8 years, 4 months, displayed signs suggesting virilism. Adrenal tumor was suspected, but exploratory operation revealed no adrenal enlargement. The discrepancies, when compared with the other two patients, were lack of increased statural growth, no change in voice, and only moderate enlargement of the clitoris. Her behavior was masculine.

Discussion

The clinical manifestations of the three cases vary considerably, but the factors common to all of them are symptoms appearing in early childhood; all females; premature sexual development; virilism; rapid growth; evidence of disturbance of adrenal function; normal gonads, and lack of evidence of tumors in the region of the third ventricle or pineal gland; no increase in androgens or estrogens.

Pseudohermaphroditism was eliminated from the diagnosis because the children were normal at birth. In Case 1 the adrenal tumor might have been present at birth, though no symptoms indicated it until the third year of life. In Case 2 the metastatic tumor in the adrenal could not have preceded the visible lesion on the cheek discovered at the age of 4 months. In Case 3 the time of increased adrenal activity remains indefinite, the signs of virilism were less conspicuous, and the diagnosis of virilism may be questioned.

Sex precocity is more frequent in the female. All of our patients were females. In a previous report by one of us (R. L. S.) females predominated.

The age at which functioning sexual organs developed varies widely. The accepted average of 13 to 14 years is computed from a wide range. One hesitates to state the earliest age at which sexual development may be considered normal, but he may be guided in the individual problem by comparing general body development and function. In the three cases reported, sexual development may be considered premature because it is not proportional to the other structures and functions. Prematurity was manifested by the rapid development of the genitals, rapid growth, and osseous development.

Virilism in the female signifies sex reversal and is comparable with sex precocity in the male. It was manifested in all three patients by change of voice (most conspicuous in the patient in Case 1), hirsutism, enlarged clitoris, masculine contour, and masculine behavior. Accepting the criteria for diagnosing virilism as the appearance of at least two of the signs (change of voice, enlarged clitoris, and hirsutism), the patients in Cases 1 and 2 qualify. In the third patient (Case 3) hirsutism was conspicuous, the enlargement of the clitoris was only moderate, and the voice was not changed. In retrospect, this patient should have been observed longer before operation was advised. Negative findings in the adrenal and ovary facilitated the subsequent treatment.

Regarding the operative approach to a suspected adrenal tumor, the abdominal incision offers several advantages. By the lumbar route,

both sides must be opened to locate the tumor, to insure that one adrenal is normal, and other viscera cannot be explored. A small incision at the level of the umbilicus permits exploration to determine the location of the lesion. If an arrhenoblastoma is found in an ovary, the incision can be extended downward to expose the ovary satisfactorily. If an adrenal tumor is found, the incision may be extended upward and the adrenal can be satisfactorily approached. Thorough exploration affords valuable information that would be lost if the lumbar route were used.

Mild degrees of virilism are not uncommon, but among all of those observed, only the two reported herein have been definitely associated with adrenal tumor. The series is too small to permit assuming definite criteria for the differentiation of virilism with and without adrenal tumor. My impression at present is that those with tumor tend to progress steadily and more rapidly than those with a milder type of virilism. It is hoped that as more cases accumulate in the literature, the means of preoperative diagnosis will become more accurate.

Discussion

DR. J. P. GREENHILL, CHICAGO, ILL.—At the present time the subject of *pubertas praecox* or sex precocity is in a state of confusion. In many cases of sexual precocity the etiology can be detected and removed, but in a large number the cause cannot be found except at autopsy. Some cases are associated with signs of virilism such as the ones reported by Pratt, but in most instances of sex precocity virilism is absent. Likewise, whereas adrenal tumors were present in Pratt's cases, the majority of cases of *pubertas praecox* have no involvement of the adrenal gland.

A survey of the literature reveals numerous case reports and a few reviews of the reported cases with attempts at classification and explanation. There is no semblance of unity concerning the total number of cases reported. One author¹ maintains that more than 500 cases have been reported, whereas only four years previously two other authors² were able to collect only eighty cases from the literature. According to Dennis, premature puberty is preceded and accompanied by an acceleration of skeletal development and of ossification. Therefore children who have reached puberty at a very early age are far above the age standards in respect to all body measurements. Their bodily proportions resemble those of the adult, but the development of their nervous system seems unaffected by these changes and is compatible with their chronological rather than their physiologic age. A study of twenty-five children who reached puberty before 2 years of age revealed that they did not walk earlier than other children. Of Keene and Stone's collected eighty cases of all types of *pubertas praecox*, 60 per cent were girls.

The causes of sex precocity may be divided into the following four groups:

1. Those associated with adrenal tumors like the cases reported by Pratt. In this group there are more females than males. Most of these cases have associated virilism, such as hirsutism, enlarged clitoris, and marked muscular development.

2. Those due to ovarian tumors. Various types of ovarian neoplasms have been encountered including malignant teratoma and carcinoma, but in most cases the tumor is of the granulosa-cell or of the theca-cell type. Young girls who have granulosa-cell tumors menstruate but they do not ovulate; hence they cannot become pregnant. Lull³ claims that only sixteen cases of ovarian tumors have been reported in very young children who showed signs of precocious puberty. He reported two cases of his own.

3. Those associated with lesions of the brain. This is a heterogeneous group because it includes cases of *pubertas praecox* associated with ventricular cysts, tumors of the tuber cinereum, tuberos sclerosus of the brain but especially hydrocephalus and disturbances of the hypophysis and pineal body. Among 177 cases of pineal body tumors collected from the literature by Bing, Globus, and Simon⁴ there were

twenty-one cases of *pubertas praecox* but only one was in a female. Dorff and Shapiro⁵ suggested that chronic increased intracranial pressure with compression of the hypothalamic-infundibular-hypophyseal pathway is the starting point of the development of the precocious state. Kraus, quoted by Dorff and Shapiro,⁵ maintained that in patients with neoplasms of the brain and meninges and in patients with chronic hydrocephalus associated with chronic increases in intracranial pressure, the anterior lobe of the pituitary gland becomes either overactive or underactive, depending on the particular changes that have occurred in the hypothalamic region. In 83.3 per cent of Kraus' cases with increased intracranial pressure, the ovaries showed microcystic degeneration. In 60.3 per cent the follicle-stimulating hormone was increased in the blood and urine. Some patients gave positive Aschheim-Zondek tests. In the group of cerebral lesions Novak includes Albright's syndrome which consists of disseminated fibrosis of the bone, extensive patchy, cutaneous pigmentation, precocious growth and (in females) precocious puberty. Albright⁶ found the ratio of females to males to be 3:2. Up to 1934 thirty-four cases of Albright's syndrome had been reported in the literature.

4. The *constitutional type* named and graphically described by Novak.⁷ I agree with Novak that this is the most common type of precocious puberty. These patients develop a very early puberty without detectable disturbances in any endocrine gland or any organ of the body. Novak believes that the reason these children skip part or all of their childhood is that there is a disturbance in certain genes. The remarkable facts about the constitutional cases of precocity are that the children remain healthy and live on as do the girls who begin puberty at the customary times and they not only menstruate but also ovulate at least soon after the menses are well established. Therefore they are capable of becoming pregnant at an early age. I further agree with Novak that all the cases of pregnancy which have been reported in girls from 5 to 9 years of age have occurred in constitutional cases of sex precocity. While great interest is centered in the group of constitutional cases by the parents, siblings, relatives, and doctors during their early childhood, after the age of 10 or 11 these youngsters do not differ from the girls who have had their puberty at the proper time.

Of what practical value is this knowledge of the classification of the causes of sex precocity? The most curable group is that due to granulosa-cell and theca-cell tumors, but such cases are very rare. In most of these cases removal of the ovarian neoplasm results in cure, but we must remember that these tumors are malignant. The second group of cases where at least some of the patients may be restored to their normal sex status is the type associated with adrenal tumors. Hence in cases where no ovarian tumor is palpable and certainly when signs of virilism, particularly hirsutism, are present, it is justifiable to perform an exploratory operation in the hope of finding an adrenal tumor. The most hopeless cases are those in which there is a lesion of the brain. Even if a correct diagnosis can be made before death, the prognosis is grave.

In the constitutional group of cases no treatment can be carried out to overcome the sex precocity. However, since the secondary sex characteristics of these youngsters make them attractive to mature boys and adult men, they must be carefully guarded against coital indulgences. Not only are there dangers of venereal infection and psychic effects, but also risk of pregnancy because these children ovulate in contrast to the cases in the other groups. Since sex precocity is more common than is generally believed, we as gynecologists should acquaint ourselves with the available knowledge of this subject so that we can cooperate with the pediatricians and parents in the care of these children.

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DR. EMIL NOVAK, BALTIMORE, MD.—The distinction which gynecologists most frequently must make in these cases of precocious puberty is between that of the granulosa-cell tumor variety and that of constitutional type. The other possible causes are, as a rule, readily eliminated, sometimes almost at a glance. For example, in the adrenal cases, such as those reported by Dr. Pratt, a precocious puberty characterized by heterologous sex characters is exhibited. They show hypertrichosis, but the hair growth involves not only the genitals and axillae, but usually other parts of the body, like the abdomen or extremities, with at times tufts of hair on the back. In the granulosa and constitutional cases, on the other hand, the hair is apt to be limited to the genitals and axillae, just as it is in the girl at normal puberty.

Again, in the adrenal cases there is often marked hypertrophy of the clitoris, which is never seen in the constitutional or granulosa-cell tumor cases. Finally, the precocious development seen in the adrenal cases is associated in only a minority of cases with precocious menstruation, a characteristic manifestation in the other two chief varieties.

The pineal tumor group, the tumor usually being a teratoma, does not concern the gynecologist, since, with one possible exception, all known instances have occurred in males. Furthermore, the precocious changes are probably due to involvement of certain brain areas rather than of the pineal body itself. Other causes of precocious puberty, such as tumors of the hypothalamic areas, are commonly characterized by definite cerebral symptoms far graver than the precocious sex changes.

The granulosa-cell tumor variety presents changes like those we might expect from the administration of large amounts of estrogen to infants or young children, and the menstrual bleeding which they show is purely estrogen-induced and not of course associated with ovulation. In this important respect they differ from the far more common cases of constitutional or genic type, in which ovulation does not occur, and precocious pregnancy is therefore possible. Unless one can actually palpate an enlargement in one or other ovary, one should lean toward the latter diagnosis. Dr. Greenhill has kindly alluded to my recent publication on this subject in which a report was made of nine such cases which I have observed. Another instance has been encountered since the publication of this paper.

HABITUAL ABORTION*

JAMES KNIGHT QUIGLEY, M.D., F.A.C.S., ROCHESTER, N. Y.

THE inability of a woman to pursue a pregnancy to its fruition, the birth of a child which has a chance of survival, is of importance not only to the individual involved but also to a nation whose birth rate is low. To the individual, a repetition of this accident several times is a keen disappointment bordering on the tragic, and in her physician it creates a sensation of frustration and of his inadequacy. Taussig says: "How much human happiness is involved in the saving of these fetal lives! What greater triumph than to bring to pass the birth of a living child by a mother who for years has had her hopes thwarted by habitual abortions!"

The causative factors of repeated abortions are not well understood, but, according to present ideas, might be summarized in three groups:

1. *Maternal.* a. *Pelvic Organs.*—Malpositions, tumors, infections, lacerations of the cervix, and an endometrium incapable of proper decidua formation permitting satisfactory nidation.

*Read at the Fifty-Sixth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 7, 8, and 9, 1944.

b. *General*.—Syphilis, toxic agents such as alcohol, lead, and phosphorus, anemias, dietetic deficiencies (avitaminosis), and endocrine disturbances; under this last heading can be included hypothyroidism and hyperthyroidism, and deficiencies or imbalance of estrogen and corpus luteum, and possibly blood incompatibility between the husband and wife. We may yet learn that there exists a condition similar to the Rh factor responsible for erythroblastosis.

2. *Paternal*.—Excessive sexual activity or sexual exhaustion. Infections: syphilis, gonorrhea, prostatitis. Endocrine disturbances: hypothyroidism and hyperthyroidism.

3. *Ovum*.—A condition of the ovum incompatible with its continued uterine life; this has been called defective germ plasma. Hertig and Edmonds found abnormal ova in 47.4 per cent of 53 consecutive cases of spontaneous abortion. Whether these abnormal ova are due to abnormalities in the germ cells or to developmental environment such as an unhealthy decidua is unsettled. It is possible that either or both may be operative. If this is true, it would seem that the latter might be susceptible of correction.

Management

Prior to the present treatment of repeated abortions, the care of this condition was limited to months of absolute bed rest. This was often ineffectual and women aborted during long periods of such immobilization.

The husband and wife should be subjected to as painstaking investigation as that undertaken in the diagnosis of sterility. There is a correlation between these two conditions. Women infertile because of ovarian failure, who later conceive, often abort due to the cause of their sterility. Appropriate treatment should follow the discovery of any possible causative factors. The correction of a retrodisplaced uterus is best done before conception with the fitting of a pessary. Too much manipulation of a pregnant uterus may defeat our object. In the majority of cases, however, no local causes are found, and the management resolves itself into measures aiming to correct deficiencies of endocrines and vitamins. The patient should be instructed to refrain from exertion on the days of her first four missed menstrual periods. Intercourse should be interdicted for four months. The entire subject should be carefully explained to her; she should be encouraged, but no absolute promise of success should be given. Because of the intense desire for children, these patients are usually cooperative.

Progestin by intramuscular injection, 5 units every four days, is begun after the first missed period. In case of any bleeding or pelvic pain she should be put to bed and the frequency of the progestin injections increased. Morphine is not indicated, but simple sedatives can be used. Peroral administration of anhydrohydroxyprogesterone offers a more convenient method of therapy. Hamblen believes it to be as efficient as the intramuscular injection of progestin. Soule, Krohn, and Greenblatt concur in this. Still another method should, because of its simplicity and economy, receive further trial, that of pellet implantation described by Mishell. Interruption in the third trimester of pregnancy initiated by contractions or rupture of the membranes may be due to the preponderance of estrogen. Progestin is indicated and may act as an antagonist to prevent premature labor.

Results

Of the 30 patients treated, 28 delivered living, normal children, 22 at full term and 6 between 7½ and 8¾ months.

TABLE I. RESULTS IN THIRTY CASES OF HABITUAL ABORTION TREATED WITH PROGESTIN

| NO. | LENGTH OF PREVIOUS PREGNANCIES IN MONTHS | WEEK TREATMENT BEGUN | WEEK TREATMENT STOPPED | ABORTION THREATENED THIS PREGNANCY* | WEEK THREATENED | RESULTS |
|-----|--|----------------------|------------------------|-------------------------------------|-----------------|-----------------------|
| 1 | 3 | 4 | 17½ | P | 10 | 9 mo. normal child |
| 2 | 3½, 9, 9, 1½, 3 | 8 | 35 | P and H | 9 | 8½ mo. normal child |
| 3 | 9, 9, 2, 3 | 14 | 16 | P | 12 | 9 mo. normal child |
| 4 | 4½ | 5 | 26 | H | 13 | 9 mo. normal child |
| 5 | 9, 9, 9, 3 | 8 | 15 | P and H | 9 | 9 mo. normal child |
| 6 | 9, 8, 2½, 3, 3, 2½ | 7 | 21 | | | 9 mo. normal child |
| 7 | 9, 7 | 5 | 35 | P | 6 and 31 | 8½ mo. normal child |
| 8 | 9, 4, 3½, 9 | 5 | 9 | H | 7 | 9 mo. normal child |
| 9 | 5, 8, 8 | 6 | 31 | P and H | 12 | 8 mo. normal child |
| 10 | 3, 3, 3 | 5 | 33 | P | 5 | 9 mo. normal child |
| 11 | 4½ | 7 | 28 | P | 8 | 9 mo. normal child |
| 12 | 4, 9, 2, 3 | 5 | 16 | H | 7 | 9 mo. normal child |
| 13 | 9, 2½ | 7 | 14 | | | 9 mo. normal child |
| 14 | 3, 4½, 3, 3½ | 5 | 16 | P and H | | 4 mo. aborted another |
| 15 | 9, 9½, 3½, 3½, 3½, 3½, 3½ | 10 | 17 | | | 9 mo. normal child |
| 16 | 1½, 2 | 5 | 23 | H | 16 | 8½ mo. normal child |
| 17 | 5, 9, 2, 4 | 7 | 21 | | | 9 mo. normal child |
| 18 | 2½, 2½ | 6 | 34 | P | 25 | 9 mo. normal child |
| 19 | 7½, 4½ | 5 | 16 | H | 5 | 8½ mo. normal child |
| 20 | 2½ | 7 | 17 | P | 14 | 9 mo. normal child |
| 21 | 8, 9½, 3 | 3 | 17 | | | 9 mo. normal child |
| 22 | 2, 3½, 9, 2 | 5 | 26 | | | 9 mo. normal child |
| 23 | 9, 5, 9, 2 | 4 | 12 | P and H | 5 | 9 mo. normal child |
| 24 | 2½, 3½, 2 | 5 | 15 | P | 6 | 9 mo. normal child |
| 25 | 9, 2, 2 | 4 | 25 | P | 17 | 9 mo. normal child |
| 26 | 9, 9, 2, 3½, 2 | 6 | 24 | | | 5 mo. missed abortion |
| 27 | 9, 2, 2, 3 | 4 | 26 | | | 9 mo. normal child |
| 28 | 3, 3, 3 | 6 | 32 | | | 8½ mo. normal child |
| 29 | 4 | 6 | 30 | | | 9 mo. normal child |
| 30 | 9, 3, 4 | 11 | 30 | P and H | | 7½ mo. normal child |

*P = Pain.

H = Hemorrhage.

TABLE II. COLLECTED RESULTS IN PROGESTIN THERAPY IN HABITUAL ABORTION

| AUTHOR | CASES | FAILURE | SUCCESS | PER-CENTAGE SUCCESS |
|---|-------|---------|---------|---------------------|
| Kotz, Parker, and Kaufman (collected cases) | 273 | 57 | 216 | |
| Kotz, Parker, and Kaufman (own cases) | 42 | 5 | 37 | |
| Davis, Hamblen, Cuyler, and Baptist | 24 | 8 | 16 | |
| Mason, L. W. | 19 | 2 | 17 | |
| Quigley, J. K. | 30 | 2 | 28 | |
| Total | 388 | 74 | 314 | 80.9 |

One failure, Case 26, was that of a woman whose first two pregnancies terminated at term uneventfully, but whose third, fourth, and fifth pregnancies resulted in spontaneous abortions at between two and three months. During her sixth pregnancy she received progestin from her sixth to twenty-fourth week, when she had a missed abortion of a three and one-half to a four months' fetus.

Another patient, with a history of four previous abortions and no living children, aborted at the fourth month and since then has had the same experience under the care of another physician, making her sixth abortion, all occurring at the end of the fourth month. Five patients required progestin to prevent the onset of labor at seven months; three of these delivered in the ninth month and two at full term. Early threat to abort was common in this series; five had hemorrhage only, none had pain only, and five had pain and hemorrhage.

Of those cases having had only one previous abortion, two had been treated for sterility, a condition akin to habitual abortion and in which abortion can be predicted. The others were included for two reasons: symptoms of abortion in the present pregnancy, or previous premature labors. Uterine curettement was done in three cases of this series in the hope that an endometrium would result more favorable to nidation. Four having metabolism rates below normal were given thyroid extract. All cases received progestin by intramuscular injection in doses varying from 1 to 5 units every three or four days.

The incidence of habitual abortion is not high; the number of cases reported by one physician from his own experience is limited. For this reason, I have collected the published experience of many others who have employed progestin prophylactically.

Discussion

The object of this report is not to contribute anything new to the understanding of this condition, but to briefly review a series of cases which were treated successfully, it is believed, by a method which had received wide acceptance, but which recently has been challenged. Taussig in his book *Abortion* says: "No method of treatment for the prevention of abortion has been attended with as much success as that of endocrine therapy." It is true that much of the criticism of this therapy has been directed against its employment in threatened abortion rather than prophylaxis against habitual abortion; nevertheless, the principles upon which it is founded apply to both conditions. Paine questions the validity of the experiments by Moir to prove the sedative effect of progestin upon the uterine musculature. This assumes that the only function of the corpus luteum is to prevent uterine contractions, ignoring its action in favoring nidation. Aside from laboratory evidence progestin is known to relieve afterpains and false labor pains (painful Braxton-Hicks contractions), both due to uterine contractions. Hamblen, after pregnanediol determinations in pregnant women, concludes as a result of these observations that the administration of progestin is not indicated. "Any beneficial effect, which therapy with progesterone possesses in the treatment of habitual abortion, cannot be explained upon the basis of its complementing deficits in progestin pregnanediol metabolism."

Proof of the sedative effect of progestin upon the uterus is not adduced here except in a clinical manner. Krauss, Moir, and others have demonstrated this by the intrauterine use of the bag.

Coincidence might be cited as a reason for the birth of living children to women who had previously had from two to five spontaneous abortions; in other words, these pregnancies untreated would have pursued a normal course. The results in at least twelve of these cases were too striking to admit of this explanation. Aside from this, two of these women subsequently tried to go through the term without treatment and failed.

It has been claimed that the rest prescribed for these patients might be the therapeutic factor. Two arguments against this are: First, it was minimal. The only bed rest advised was for a part of the time each day of the first three missed menstrual periods and not all of

them had even that. Second: We all have seen women, on absolute bed rest for four or five months, abort while in bed.

Objection to the prevention of habitual abortion has been raised on the ground that abortion is Nature's method of disposing of imperfectly formed fetuses, and therefore the preservation of pregnancy should not be encouraged. There is, of course, this possibility, a risk which must be taken. There is much evidence in favor of an increased percentage of fetal abnormalities in children born at term after threatened abortion early in pregnancy. This tendency probably does not exist to the same degree in habitual abortion as in threatened abortions. Fortunately there were no abnormal children in this small series. Had this fear been acted upon, few of these twenty-eight couples would probably have children today. Another objection is that of the cost of the substances employed. Were this compared to the expense involved in the adoption of a baby, it would be insignificant, and most women prefer a child of their own. One more criticism is that this plan does not always succeed. Is there any therapeutic measure that is infallible? Absolute promise of success should never be made, but even a 50 per cent chance would be accepted by most women.

The only cases of threatened abortion here reported are those cases of habitual abortion under prophylactic treatment where hemorrhage or pain or both occurred. The threat in all but two of these subsided and they went on to term resulting in the birth of normal children.

The prophylactic treatment of repeated abortions instituted as soon as pregnancy is diagnosed is quite a different matter from the treatment of threatened abortion. Both Mall and Hertig have shown that approximately 50 per cent of all early abortions are due to fetal fault or imperfection. It is also known that fetal death antedates by days or weeks the onset of symptoms in many cases. From this we can conclude that treatment by rest, sedative, progestin, or any other means does not offer as much hope of success as treatment begun before the appearance of symptoms.

To determine the viability of the early fetus, Rutherford does an aspiration biopsy of the decidua of the lower uterine segment and says that the normal viable fetus is not apt to be expelled by the instrumentation involved. There should be some hesitancy in adopting this diagnostic procedure in the repeated abortion case where little manipulation is needed to inaugurate hemorrhage or contractions or both.

Conclusions

1. Twenty-eight of the thirty women who were habitual aborters under treatment went to full term or near it, and gave birth to normal children.
2. Uterine curettage was done in three cases, and in four cases thyroid extract was given.
3. Successful termination of a pregnancy treated prophylactically against abortion does not guarantee full term in a subsequent pregnancy untreated.
4. Two possible fields for further investigation as to the cause of repeated abortions are: (1) The quantitative relation between the

estrogen and corpus luteum secretions. (2) Blood incompatibility of husband and wife similar to the Rh factor in erythroblastosis.

5. While there is some question from experimental evidence as to the value of progestin to prevent abortion, the writer feels that the results reported by many careful observers warrant its continued use at least until a better method is evolved.

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Discussion

DR. A. K. PAINE, BOSTON, MASS.—Dr. Quigley frankly states that his employment of progesterone was based on numerous published reports of its successful use in the treatment of habitual abortion. Because he entered into no extended discussion of the rationale of progesterone therapy in such cases, discussion perhaps could properly be limited to case reports, in general and in particular.

A review of thirty-six articles on habitual abortion discloses an interesting variety of therapeutic agents. Exclusive of the usual bed rest, sedatives, etc., the list includes the progesterones, vitamins E and K, thyroid, placental extract, anterior pituitary-like hormone, estrogens, pregnancy serum, sodium iodide, and organic arsenicals. Exclusive of the progesterone series, the average success rate of this intriguing therapeutic display was approximately 80 per cent. Progesterone on the other hand, used alone or in various combinations, even though some authors reported a 100 per cent success, curiously had an average success rate of only 74.5 per cent.

The extract of corpus luteum series is not included in these progesterone percentages because of some question as to whether it represents a source of the latter, or something else.

As long as results are satisfactory, it is probably captious to wonder about combinations of therapeutic agents, progesterone with vitamin E, thyroid, etc., and to which in such instances the success should be credited. We are thankful that in Dr. Quigley's cases this question arises infrequently. Three had a prior curettage. Most of us, I suspect, would be glad to give full credit to the progesterone, hoping thereby to forget that not so long ago a prior curettage was a *sine qua non* in the treatment of habitual abortion. But what of the four cases with an accompanying thyroid therapy? We have been repeatedly reminded of the importance of thyroid dysfunction in these cases, and White reports a 90 per cent success with thyroid extract.

Studying case reports, one is conscious of another insistent question, rather sophomoric perhaps, but what is meant by the term habitual abortion? Hertig suggests that a patient should have at least *two* prior consecutive spontaneous abortions before she can be termed an habitual aborter. Javert and Stander recently stated that their criterion was *three* prior consecutive abortions. Is not something involved here beyond a mere academic interest in terminology from the standpoint of dependable statistics? Many reported series with high success rates include cases which have had but one previous abortion.

A pregnancy with a history of a previous abortion, premature delivery, or a long period of sterility certainly furnishes reason for considerable anxiety and

the physician is justified in employing procedures he believes may minimize unfortunate possibilities. When such a pregnancy terminates successfully, it is natural perhaps to assume or believe that, without the specific treatment, the patient would have aborted. If she had aborted, she would then be an habitual aborter. But the use of such intangibles and the assumptions based thereon to attest statistically the value of some treatment is open to a good deal of question. It stands to reason that success percentages will be measurably higher if cases are included as such, which are not in fact repeated aborters.

There also appear frequently in reports of some highly successful treatment for threatened abortion numerous cases which *did not have* the most common, characteristic, and usually the *first* symptom of threatened abortion, namely bleeding. Dr. Quigley is to be commended for excluding this questionable group from his series.

We have at present no convincing evidence that all or any habitual abortions result from a progesterone deficiency, nor have we any definite evidence that progesterone administration will correct such a deficiency if it exists. On the contrary, such evidence as we have, Hamblen's work for instance, seems to indicate it will not.

The empiricism which progesterone therapy at present represents could well remind us that for a time, based on successful case reports, an early commercially available anterior pituitary-like hormone was also widely exploited as a last word in the treatment of habitual abortion.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—In 1934 when we began to get interested in progestin, one of the drug companies went to considerable expense to produce what was called "corlutin" which was standardized by the use of the virgin rabbit's uterus. Two of my associates and I started to use it. We soon began to see that in women who were beginning to abort and received these injections, something happened. In about 1934 we reported forty cases, some of which were habitual abortions, with a very much higher percentage of salvage than any of us had seen. We had 86 per cent salvage in a group of women who had had 85 per cent failures in previous pregnancies.

About the following year I began some studies with an intrauterine bag which was inserted into a seven-day puerperal uterus connected to a kymograph. I injected an ampule of pituitrin which was followed immediately by uterine contractions. I waited for about five minutes to get these contractions well established and then I injected some of this "corlutin." The uterine contractions within five minutes stopped and remained so for about twenty minutes. I used another ampule of pituitrin and another and they did not start again. I drew the conclusion that this material inhibited contractions of the uterus produced by the posterior lobe pituitary extract. For the first time I felt that the clinical results we had obtained had a foundation that could not be ascribed to wishful thinking.

The expense of the oily preparation was too great and we wondered whether the cheaper, watery suspension of the corpus luteum had this contraction inhibiting material in it. We used the watery extract and found that by using more of the extract (about 10 to 1) we got practically the same response. When we first began to use the oily extract it was furnished to us in $\frac{1}{25}$ of a rabbit unit. We asked for a more potent ampule and they made $\frac{1}{10}$ of a unit and with that we got better results. Then we thought that about 1 c.c. of the watery extract would be about equal to the $\frac{1}{10}$ unit of the oily preparation. So we continued our experiments using larger volumes of the extract of the corpus luteum, we found that we got good results with the watery extract and that the cost to the patient was less.

We then collected a series of close to 500 cases of threatened abortion in the County Hospital and the Research Hospital and in one private practice. We found that the salvage from abortion amounted to about 85 per cent in the three groups. Then we stopped using the lutein extract at the County Hospital but treated the patients otherwise exactly as before. We found that the salvage dropped to only about 40 per cent. Then we went back to the injections and found that we got the same results as before.

Our conception of the value of this material is therefore based on clinical experience, and on the evidence that by the use of both the aqueous and the oily extractions of corpus luteum you can stop human uterine contractions stimulated by pituitrin. We feel that these contractions are an important factor in the mechanism

of abortion. Fifteen per cent of the cases still aborted and I think that will always be true. I do not think any one can every stop abortion cases 100 per cent.

This report of Dr. Quigley is exactly what one would expect if he has had any experience with this treatment in this condition. All over the country, men are using this material and with very good results. Personally, my mind is made up on the basis of what I have told you. Both clinically and in the laboratory this material gives results that I have not seen in the treatment of habitual or threatened abortion when it is not used.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—About twenty-four years ago I reported a series of seventeen cases of what we considered true habitual abortion. In this series, all of the patients were found to have hypothyroidism. All were put on adequate doses of thyroid extract and fourteen of the patients went through to term. Two promptly aborted within two weeks after they had voluntarily stopped taking thyroid. One of these two later continued the treatment throughout pregnancy and was successfully delivered. Several of these and subsequent patients have had more than one baby while on thyroid therapy. It goes without saying that this extraordinary percentage of success has not been maintained.

With regard to the causes of abortion one of our histologists has made an intensive study of all our suitable material, and found that about 85 per cent of the spontaneous abortions showed definite evidences of fetal or placental maldevelopment. Only about 15 per cent were due to apparent changes in the maternal organism of one sort or another. In studying the rare cases of true habitual abortion, however, there was a very low percentage of fetal abnormality and a slightly higher percentage of maternal abnormality. One might expect habitual abortion to be due to maternal disease or dysfunction unless, possibly, the woman is continuously producing defective ova.

As to the effectiveness of progesterone, I confess that on going over my first series, I found the results similar to those in the untreated series. Recently I learned from Dr. Falls that progestin extracted from the corpus luteum is much more effective than the synthetic product which we had been using.

When it comes to the general subject of abortion, not necessarily habitual abortion, there are many types of abortion due to fetal abnormality which cannot be corrected by progesterone. Neither would it influence the type of abortion due to such accidents as placenta previa or abruptio placentae, except in so far as it might lessen the irritability of the uterus to the extravasation of blood between uterine muscle fibers. It will be necessary to segregate as completely as possible the cases of abortion which are actually due to myometrial hyperirritability before a real evaluation of the efficiency of progesterone can be made.

DR. FRANK E. WHITACRE, NEW ORLEANS, LA.—The importance of the effect of coitus on abortion is not given its proper emphasis. Several years ago on our service in Peking, I appointed one of our staff women to question carefully these patients as to how many hours prior to the onset of a spontaneous abortion coitus had taken place. In a remarkable number, although exact figures are not available, there was a history that a few hours before spontaneous abortion coitus had occurred.

Coitus is mentioned in articles and textbooks, but not as one of the important causes. We know that abortion is more apt to take place at the time the patient would menstruate if not pregnant. The progesterone level may be affected at that time and there may be a hormonal response from the act which may raise the estrogen level, stimulating uterine contractions. Therefore, it is possible that many of these abortions are on a hormonal basis from coitus, rather than merely mechanical stimulation.

I was able to show recently the marked effect of psychic factors on the hormonal levels, under the title of "War Amenorrhea," in describing the effect of the bombings on women in Manila. I feel that the effect of coitus as a stimulant in spontaneous abortions is important.

DR. ARTHUR H. BILL, CLEVELAND, OHIO.—In Dr. Quigley's paper and in the discussions which have followed, I have been surprised that so little was said about the retroverted uterus. This complication is tremendously overlooked and

even belittled by obstetricians who are treating these cases. In my experience, retroversion is one of the most common causes of miscarriage. I would never think it proper to leave a pregnant uterus in retroversion. The position should always be corrected and the uterus held in position by a retroversion pessary. As valuable as the form of treatment that has been described may be, I have personally seen many cases in which there have been repeated miscarriages in patients who have been treated by all these forms of therapy with no success while the presence of a retroverted uterus has been entirely overlooked. Patients of this kind may wear a pessary and go through a normal pregnancy without any medication.

Sometimes a patient may, on examination, be found to have a perfectly normal pelvic condition when she is not pregnant, but when she is six or seven weeks pregnant to have a retroversion. Furthermore, I would not take for granted that the patient will not have a retroverted uterus a week or two later just because it is normal on the first examination of pregnancy.

As valuable as this treatment is, and I believe that there is value in progesterone, one should not depend entirely on medication but should always correct a retroversion of the uterus.

DR. QUIGLEY (closing).—I did mention retroversion of the uterus in my paper and said that there should be care in looking after this condition, but perhaps did not emphasize it sufficiently.

Dr. Cooke's discussion was very interesting to me in regard to pathology of the ovum because it coincided with an opinion I have that this is less common in these cases of habitual abortion than we have thought.

I do not want to give the impression that I think giving progesterone is the only treatment for habitual abortion. All of my patients having a low metabolism rate were given thyroid. There is a function which progesterone performs aside from preventing uterine contractions, for it plays some part in nidation and has something to do with decidua formation.

DUPLICATION OF RIGHT KIDNEY PELVIS AND URETER WITH EXTRAVESICAL URETERAL OPENING*

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THE presence of an ectopic ureter presents a problem for the gynecologist since the great majority of cases producing symptoms are found in females. In 1936 Furniss collected and reported 240 cases of accessory ureters with extravescical opening. These included the cases collected and reported by Kilbane, Campbell, Thom, Sargent, and others. Lowsley and Conroy have estimated that there are approximately 300 such cases on record at the present time.

Ectopic ureters are found more frequently in females than in males, the ratio being about 2:1. The reason for this is that in the female an ectopic ureter usually opens distal to the vesical sphincter and produces a dribbling incontinence, while in the male it usually opens proximal to the vesical sphincter and is therefore asymptomatic. This dribbling incontinence in females is found present since birth, but in spite of this there is normal emptying of the bladder.

*Read at the Fifty-Sixth Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 7, 8, and 9, 1944.

According to Thom's series of 117 females with ectopic ureteral openings the locations were as follows: vestibule, 45; urethra, 37; vagina, 32; uterus, 3.

Embryology

Embryologically the secretory portion or cortex of the kidney is developed from an undifferentiated and unsegmented cell mass termed nephrogenic tissue. The ureter, renal pelvis, and collecting tubules, however, are formed by a separate "anlage" in the shape of a hollow bud arising from the mediodorsal aspect of the wolffian duct. In the 4.5 mm. embryo, the ureteral bud may be seen arising from the caudal end of the wolffian duct; it lengthens and grows cranially to enter the nephrogenic tissue forming a cap around its upper end which becomes flattened as the ureter lengthens and forms the major and minor calices and collecting tubules. As further growth takes place, the ureter and wolffian duct acquire separate openings into that portion of the cloaca which is destined to become the bladder.

The presence of an accessory ureter represents a regressive variation, and its ureteral bud arises from the wolffian duct usually a short distance cranial to the normal ureteral bud. As the wolffian duct orifice descends, the most caudally placed, or normal, ureter is the first to reach its position in the bladder. Because of a rotation and a growth of the tissue between this ureteral opening and the orifice of the wolffian duct, the upper ureter is carried caudalward so that it oftentimes becomes implanted at a point below the sphincter of the bladder.

Diagnosis

A dribbling incontinence of urine, in the presence of normal bladder function, is pathognomonic of ectopic ureter when occurring in a female. In the majority of instances this symptom has been present as long as the patient can remember. In a few reported instances incontinence is present only when the patient is in the upright position. Mulholland has reported a few cases of ectopic ureter in women where incontinence was not present. Judd reported the case of a 21-year-old girl who had diurnal incontinence during her entire life but had nocturnal incontinence only during the first few years. This led to an error in diagnosis so that the first operation performed for relaxed bladder sphincter was unsuccessful.

Much patience and diligence are often necessary in locating the orifice of the ectopic ureter. Attempts to locate the orifice of the ectopic ureter by means of intravenous injections of dyes are often unsuccessful because the fragment of kidney tissue drained by the accessory ureter may be so small or its function so impaired by infection that very little or no dye will be excreted. An intravenous pyelogram which shows multiple pelves on one side, and this in the presence of incontinence, should make one suspicious of an ectopic ureter. Crenshaw states that it is not absolutely necessary to demonstrate the orifice of the ectopic ureter if there is a history of dribbling and evidence of duplication of the renal pelvis by intravenous pyelography. Cystoscopic examination will usually demonstrate that the bladder and ureteral orifices are normal.

According to Weigert's law the ureter draining the upper part of the kidney opens lower in the urinary tract, and it is always this orifice

which is ectopic. Malgras asserts that this is not always true; however, the case to be reported here does conform to Weigert's law.

Treatment

The functional value of the kidney on the opposite side should be determined before any treatment is attempted. Heminephrectomy seems to be the procedure of choice where the segment of kidney drained by the ectopic ureter is small and therefore functionally of little value. Many cases have been reported in which there is a line of demarcation between the upper and lower kidneys. Ligation of the ectopic ureter below its pelvis with a separate ligation of the arteries and veins to the upper pole, followed by a "V" grooved incision through this line of demarcation, will produce a cure. Ligation of the ectopic ureter alone has not been as widely used but has some advocates. Implantation of the accessory ureter into the bladder may be of some value where the amount of kidney tissue involved is sufficient to be worth saving or where heminephrectomy is contraindicated. However, as Lowsley points out, the accessory kidney pelvis and ureter are usually infected, and therefore implantation may lead to an intractable cystitis.

Case Report

Miss A. S., 19 years of age, was referred by Dr. E. L. Tuohy on May 6, 1941, because of incontinence of urine. She had been working as a chambermaid in a hotel, and stated that she was in good health except for the present complaint. The family history and her past history were irrelevant.

Her chief complaint concerned a urinary incontinence, which on closer questioning was found to be a constant dribbling of urine both day and night, and had been present as long as she could remember. The patient's mother also stated that the incontinence had always been present. In spite of this the patient voided apparently normal amounts of urine at regular intervals. The urinary odor, due to the constant dribbling, was very annoying and made it difficult for her to keep a job and embarrassed her in her social contacts to such an extent that she was developing an inferiority complex. Two months previously the patient's tonsils had been removed as a possible cause for this continuous dribbling.

A general physical examination was negative except for the pelvic condition, which, on examination of the vagina, revealed a relaxation of the anterior vaginal wall on the right side. On palpation, this mass felt like a dilated urethra in that it was soft and not tender. The bimanual and rectal examinations were otherwise negative. The blood counts were as follows: hemoglobin, 81 per cent; red cells, 4,180,000; white cells, 10,500. The catheterized urine specimen was negative. The blood pressure was 112/70. The Kline exclusion test was negative. Methylene blue was instilled into the bladder, and it was felt that there was very little sphincter resistance when the catheter was passed. The vagina and vulva were then packed with cotton in an attempt to locate an anomalous opening from the bladder but after a period of one hour no dye had appeared on the cotton, but a portion of the cotton was moist and had an odor of urine. Roentgenographic plates of the spine failed to reveal any evidence of spina bifida.

The following day a cystoscopic examination was performed by Dr. W. E. Hatch, and the bladder and ureteral orifices appeared to be normal. Cystograms were also made but failed to reveal any evidence of a diverticulum or other abnormality. Because of the constant dribbling of urine, it was felt that there must be an anomalous opening of some sort, so methylene blue was again instilled into the bladder and, with

the patient in the lithotomy position, the vulva and perineum were observed constantly for a period of an hour and fifteen minutes when suddenly a small bead of fluid appeared to come out of a slit in the mucosa at a point which was approximately $1\frac{1}{2}$ cm. below and to the right of the urethral orifice. A probe could be introduced into this slit for a distance of 4 centimeters. With the aid of a blunt-tipped needle a solution of skiodan was then injected into this orifice, and a filling was obtained which extended up through a very tortuous and dilated ureter into a small sacklike pelvis which was located on the upper part of the right kidney.

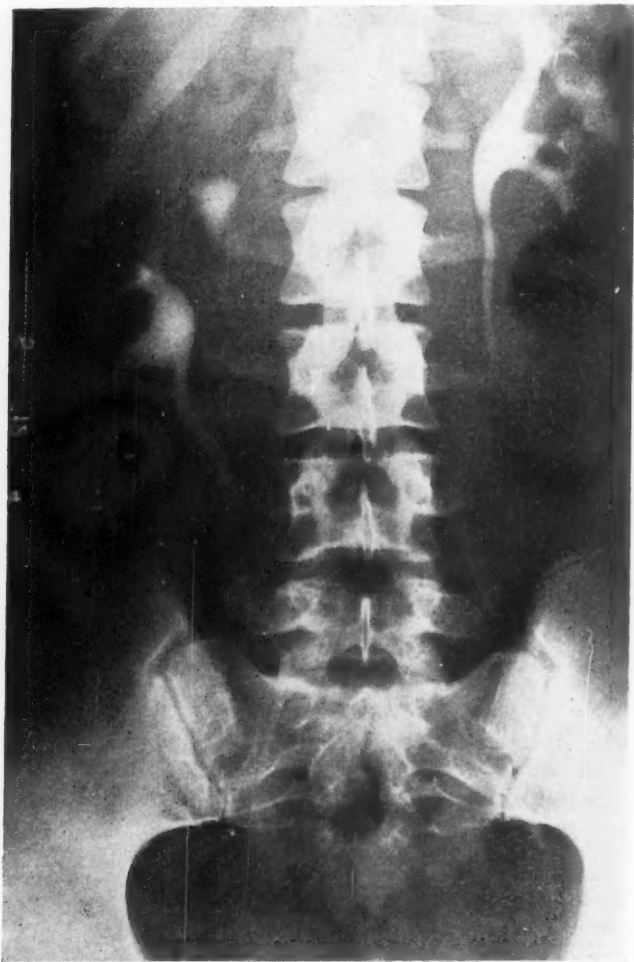


Fig. 1.—Bilateral excretory pyelogram showing duplication of the right kidney pelvis.

An intravenous pyelogram was then made to determine the presence of a functioning kidney on the opposite side. This pyelogram showed a duplication of the right kidney pelvis and ureter and a normal appearing kidney pelvis and ureter on the opposite side (Fig. 1). Retrograde pyelograms were then made with a filling of the normal ureter on the right side and also of the ectopic ureter so that both could be shown on the same plate. This showed the double kidney pelvis on the right side with double ureters, the ureter from the upper pelvis having its opening in the vestibule (Fig. 2).

Surgical treatment in the form of a heminephrectomy was advised and the patient consented. On June 3, 1941, under ethylene-ether-anesthesia, a right curved loin incision was made to expose the right kidney. The superior pole was easily delivered bringing into view the small saclike pelvis and dilated ureter. After isolation and ligation of

the blood supply to the upper part of the kidney and the ureter to the upper pelvis, a "V" grooved incision was made through an isthmus which seemed to separate the upper and lower kidneys, and the upper portion was removed. Mattress sutures were inserted to close the "V" incision, and pieces of fat tissue were interposed before the mattress sutures were tied. Urine continued to dribble from the ectopic ureter for a period of forty-eight hours following the operation, apparently due to the accumulation of urine in the dilated ureter. However, the patient made an uneventful recovery and was discharged from the hospital on the tenth postoperative day.

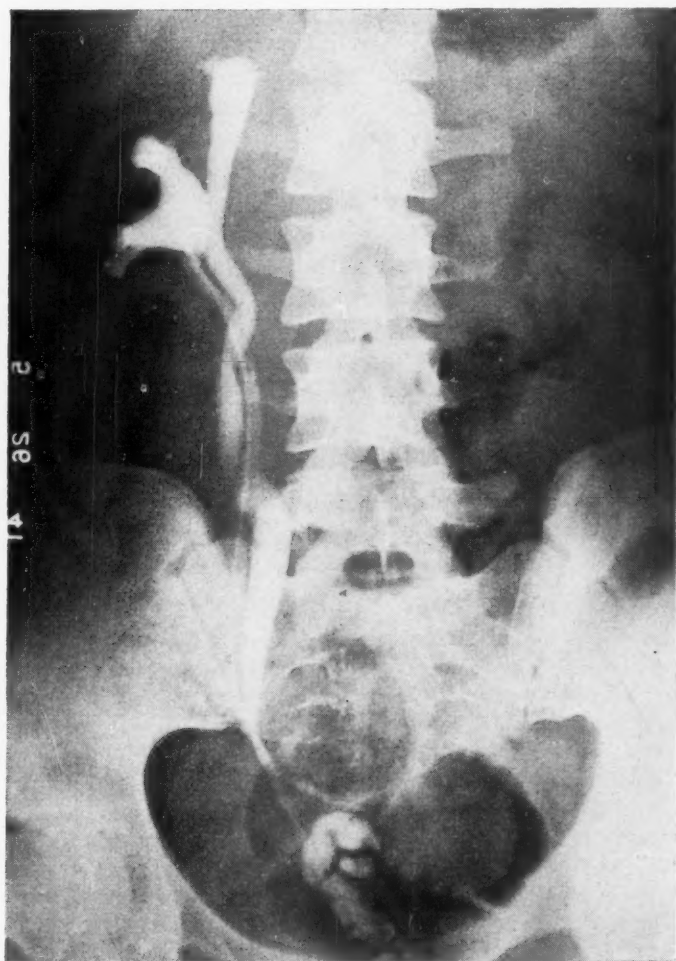


Fig. 2.—Retrograde pyelogram showing normal lower kidney pelvis and ureter and small saclike upper kidney pelvis with greatly dilated ureter.

Examination of the surgical specimen revealed a small saclike pelvis and an amount of kidney tissue equal to approximately one-fifth of the remaining kidney tissue on the right side. The blood supply consisted of one artery and one vein. There was chronic inflammation of the accessory pelvis and ureter. The submucosa of the pelvis and ureter was thickened, edematous, and infiltrated with a moderate number of scattered lymphocytes. The interstitial connective tissue of the muscular layers of the wall of the pelvis was also infiltrated with a few scattered lymphocytes.

The patient was last seen approximately two years after the heminephrectomy was performed. There were no complaints and it was apparent at that time that the inferiority complex had completely disappeared. She had become a social as well as economic asset to the family.

Conclusions

1. Constant dribbling of urine in the presence of normal bladder function should suggest the presence of an accessory ureter with an extravesical opening.
2. Intravenous urography is a valuable procedure in establishing the diagnosis of this anomaly.
3. The location of the orifice of the ectopic ureter is often difficult.
4. Heminephrectomy is the procedure of choice.

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Discussion

DR. WILLIAM A. COVENTRY, DULUTH, MINN.—This paper shows the value of patience when one must observe for over an hour to find evidence of a moist spot from an aberrant ureter. I would expect more excoriation of the vulva from such a leak, but apparently the amount of urine excreted was so small that there was total absorption by the vulva pads worn.

One might discuss whether implantation of an aberrant ureter in the bladder would be worth while, a procedure advocated by some operators. The question of tying of the ureter alone may also be raised. It seems to me the procedure carried out by Dr. Moe is probably the best, because if the ureter is infected, one is sure to have an infected bladder.

The value of proving the presence and function of the opposite kidney is apparent, especially when it is likely that if one anomaly is present, one might expect another anomaly. The tortuosity of the abnormal ureter is interesting and offers an opportunity for speculation as to its cause.

DR. B. Z. CASHMAN, PITTSBURGH, PA.—In 1928 I reported to this Association an almost identical case as that reported by Dr. Moe. My patient was 16 years of age and had a small amount of urine dribbling almost constantly as long as she could remember. The amount was not large and it was the urinous odor that annoyed her more than anything else.*

DR. MOE (closing).—Dr. Cashman calls attention in his case to a point which is very valuable, namely, the insertion of a catheter into the normal ureter on the same side as the ectopic ureter. That is of great help according to the reports in the literature, when at operation one cannot decide which ureter he is dealing with. If one is excising the accessory kidney it is not so difficult, but the men who have advocated merely ligation of the ureters have stressed the point that a catheter should be placed in the normal ureter at the time of operation.

(Conclusion of Transactions of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons)

*See *Tr. Am. A. Obst. & Gynec.* **41**: 320, 1928.

Original Communications

POSTMENOPAUSAL PRURITUS VULVAE*

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PRURITUS vulvae in the postmenopausal woman poses a clinical problem of the greatest magnitude. It is frequently encountered, is extremely discomforting to the patient and according to most reports, is seldom handled successfully. The problem is so ubiquitous and formidable that dermatologists, gynecologists and endocrinologists often refer these cases to each other. Everyone seems anxious to place this complaint in the other specialist's field.

Postmenopausal pruritus vulvae differs from the pruritus vulvae of the less mature woman in several respects, the most important being the relative infrequency of specific infections and the introduction of the atrophy process in the external genitalia. It is recommended that after pediculosis pubis, diabetes mellitus and specific local skin diseases have been excluded, that the physician approach the problem with this medical philosophy, namely, that any area of skin can be responsible for the sensation of itching if the proper combination of skin irritation and receptiveness to that irritation is present. The percentage values of the irritation and the skin's receptivity to it may vary within the combination, but the total of the two must attain a certain threshold height for the pruritic sensation to be aroused.

It becomes apparent here, that the examiner must have sufficient knowledge of gynecologic techniques to evaluate the presence and the source of any irritating discharges. Rectal discharges are seldom of importance here. They are chiefly responsible for pruritus ani. Of more interest is the possibility of urinary incontinence. A normally alert woman is seldom unaware that she is not controlling her urine properly. Usually, she is cognizant of even minute urinary incontinence, but she may not relate it to her pruritus. It is the examiner's duty to question these old women about this possibility because incessant wettings of the labia by urine is a cause of pruritus vulvae, and it can be well controlled by pessaries or proper plastic vaginal surgery.

Vaginal discharges are the chief causes of vulvar irritation. The distribution of the itching areas will often call the examiner's attention to the possibility of a vaginal discharge, although the vulva may be quite clean at that time. If the areas involved are confined to the lower halves of the labia minora and majora and to the perineum, leaving the clitoris area relatively free, one must thoroughly explore the possibility of an irritating vaginal flow. This impression may be re-enforced by information from the patient that the itching is more intense during the day than at night. Obviously, vaginal secretions will be forced out of the

*Read at a Symposium on Clinical Problems Associated with Aging, at the Annual Meeting of the American Geriatrics Society, on June 10, 1944, in New York City.

vagina and on to the perineum and labia to a greater extent when the patient is active. At night, when she is relatively inactive, less of the irritating vaginal secretion will come in contact with the external genitalia.

The principal types of vaginitis which are responsible for pruritus vulvae are the *Trichomonas vaginalis*, Monilia and senile ones. The first two varieties are only seldom encountered in postmenopausal women. They are easily identified by the trained observer, and positive laboratory identification is a simple matter. The therapy of both these conditions has become standardized and is satisfactory although often prolonged and tedious.¹⁻²

Senile vaginitis, although it is the type of vaginitis most often encountered in postmenopausal women, is not as frequent an etiologic factor of pruritus vulvae as the current literature would have us believe. One seldom sees a case of senile vaginitis in these women which is severe enough to produce a vaginal discharge sufficiently profuse to flow out of the vagina in any appreciable quantity.

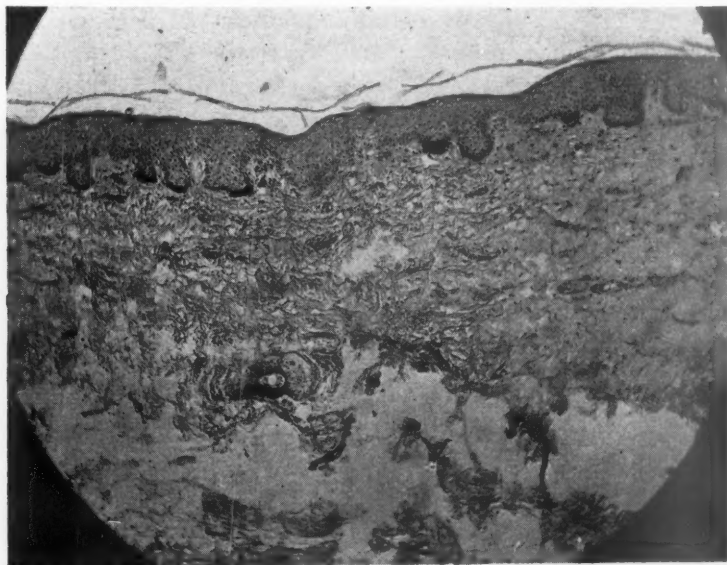


Fig. 1.—A 65-year-old woman who never complained of pruritus vulvae. The epidermis is normal. The derma is free from any sign of inflammation.

The appearance of the vagina makes the diagnosis. Corroboration is secured if a smear of the vaginal secretion reveals a Grade I cytology. Here, there is little evidence of cornification of any of the epithelial cells, a moderate number of cells from the basal layers of the epithelium is present and an abundance of leucocytes "dirty" the smear.³

This type of vaginitis yields readily to ordinary astringent tamponades and cleansing douches. Relief is obtained faster if estrogenic vaginal suppositories are employed at night before retiring. The use of estrogens by the oral and parenteral routes is not recommended. Most of these women have become accustomed to getting along on a very low systemic level of estrogens. Their estrogenic titers in the urine and blood are small.⁴ It is inadvisable to again subject their entire organism to the multiple effects of systemic estrogenic medication. Many of these older women develop annoying symptoms under these circumstances.

We prefer to use estrogens incorporated in vaginal suppositories which allow the hormones to be applied locally where their effect is most required.⁵ Thus, they are effective in concentrations which are far too low for generalized effects.

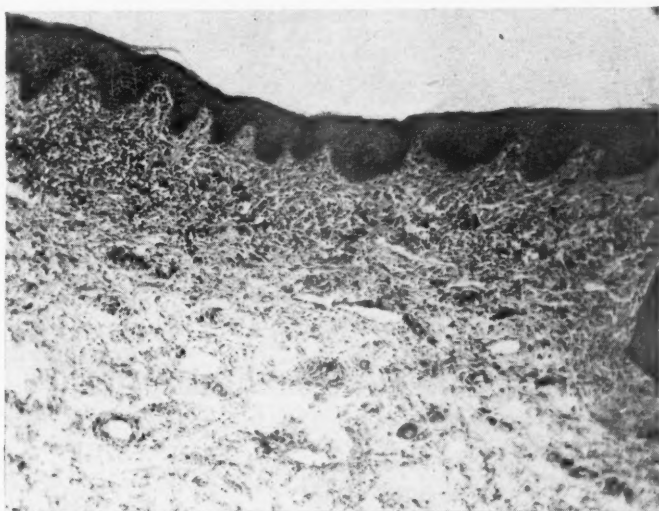


Fig. 2.—A 45-year-old woman, complaining of pruritus vulvae; macroscopically, a case of simple atrophy. Note the thin but normal epidermis. The derma exhibits a broad zone of inflammation, which extends into the papillae.



Fig. 3.—Posttherapy section after a clinical cure. The derma now shows no signs of infection.

Up to this point, we have limited our discussions to the principal vulvar irritants. However, there are a host of minor offenders, some constantly present, which assume considerable stature if the resistance of the vulvar skin declines and its receptivity to noxious stimuli increases. Among these irritants are pathogenic skin organisms, the minimal discharge from a normal vagina, an occasional few drops of urine, sweat and friction from clothes and cleansing paper. These irritants as already stated assume importance only when the resistance of the skin to infection and irritation declines.

It has been our experience to find the majority of our cases of pruritus vulvae in women past the menopause to be due to changes in the vulvar skin rather than to unusual irritating substances. It is only logical to assume that the aging process will bring about profound changes in the external genitalia, and this we have found to be true.

It is my opinion that we may recognize three types of vulval pathology in pruritus: Atrophy, lichenification and leucoplakia. These lesions have distinctive macroscopic and histopathologic characteristics, which are more or less constantly recognizable. I am unwilling to accept the traditional term "kraurosis vulvae" as a designation of a disease entity. I do not believe that a sufficiently characteristic macroscopic or microscopic picture exists to justify the use of kraurosis vulvae as an entity.

If one compares the macroscopic and microscopic descriptions which the acknowledged authorities on the subject have assigned to this condition, the most varying pictures are portrayed, and only utter confusion results. Etymologically, kraurosis means shrinking, and if the traditionalists insist on the use of the term, I recommend it to be limited to the description of accentuations of the normal vulval atrophy processes.⁶

We are unable to subscribe to the use of a single term to encompass all the conditions met with in pruritus vulvae. Chronic atrophic vulvitis, leucoplakic vulvitis and leucokraurosis are all inadequate in some respects and misleading in others.

Bonney⁷ distinguishes four stages of the disease of leucoplakia. Taussig⁸ believes that there are three stages in leucoplakic vulvitis. Adair and Davis⁹ distinguish several stages as does Montgomery.¹⁰ I should like to point out here that in order to distinguish authoritatively the stages of any pathologic process, one must obtain a series of biopsies from a given lesion in an untreated patient.

I know of no one so scientifically detached as to permit a case of postmenopausal pruritus vulvae to go untreated, while he obtained a series of biopsies. To the best of my knowledge, the histopathologic specimens have been obtained from the untreated patient only once, from patients who have had vulvectomies, from the vulvectomy specimen itself and from cadavers.

The authenticity of the description of the stages of leucoplakia of the vulva and so-called kraurosis of the vulva, or the combination of the two, may well be questioned.

In addition, I should like to point out that vulvae which macroscopically present absolutely typical conditions, often yield biopsies which are quite varied. When these slides are presented without accompanying histories to competent dermatologists, they are often unable to make the correct diagnosis which their unaided eyes would have recognized immediately. A prominent dermatologist has often assured me that, barring malignancies, if he is unable to diagnose a skin lesion by inspection and palpation, the microscope will be of little further aid to him!¹¹

It is my belief that there is a simple explanation of these conflicting facts. There are common etiological factors in most cases of postmenopausal pruritus vulvae, and the response of the skin to these factors varies with the individual. The varied macroscopic and micro-

scopic pictures one encounters in these cases are merely the resultants of the patient's capacity and manner of response to the same set of stimuli. They are not different disease processes.



Fig. 4.—A 58-year-old woman with pruritus vulvae, and a macroscopic picture of lichenification of the vulval skin. The epidermis is only moderately thickened. The pars papillaris of the derma shows an inflammatory reaction.



Fig. 5.—Posttherapy section after a clinical cure. There is some evidence of hyperkeratosis in this field. The derma is now free from infection.

As we have already pointed out, the etiological factors in these cases are always present. They are the relatively nonpathogenic skin organisms, the irritations of friction and the various discharges to which the vulva is subject. These factors become potent only when the normal processes of atrophy permit them to penetrate the weakened skin, set up a localized zone of inflammation and cause pruritus. The itching then adds the trauma of scratching to the list of offenders and the sub-epithelial infection becomes chronic. In the necessarily slow healing process which follows, we have the explanation of the lichenification and the keratosis which are the characteristic features of pruritus vulvae. This, in a nutshell, is the probable explanation of all vulval pruritus, postmenopausal.

While vulval pathology in pruritus may be divided into three types—atrophy, lichenification or lichenization and leucoplakia—a fourth type of disease, lichen sclerosus and atrophicus is sometimes encountered, but it does not merit a detailed discussion.¹²

In atrophy of the vulva, the skin eventually acquires a yellowish tinge, although in the early stages of the process, it is often dark red or purple. It seems transparent and feels thin. The hair is brittle and scanty and the term "parchment paper" may well be applied. The labia majora and minora are considerably reduced in size, and in extreme cases, practically disappear. The vaginal orifice is often narrowed to the point where only one finger can be inserted.

Microscopically, very few changes can be observed. The epithelium is usually quite thin. Stains for fat reveal the almost total absence of this material from the dermis, but elastic tissue stains show no changes from the normal.

Lichenification of the vulva presents the same picture other portions of the cutis do when they are involved in this process. The integument is thickened and becomes a mosaic of small flattened elevations, separated from each other by distinct depressions. The color varies from yellowish brown to dusky red. Occasionally, the skin has a soggy, white appearance.

The histopathologic findings are hyperkeratosis, spongiosis and acanthosis. The subepithelial tissue is edematous, and is infiltrated by lymphocytes and plasma cells.

Leucoplakia of the vulva is easily distinguished macroscopically. It presents the same appearance as leucoplakia of the mouth. It is present on the vulva as a series of slightly elevated plaques or striae, gray to blue-grayish in color. The skin or mucous membrane may be involved, and when affected, they both are thickened.

The histologic picture of the disease is much disputed.^{7-8, 12-13} As we have already stated, it is our contention that the histopathologic findings vary with the individual's response to the stimulus of relative vulval irritation. The different descriptions of the histopathologic processes may well be explained by this fact.

The epidermis in leucoplakia always shows some acanthosis and hyperkeratosis. Parakeratosis may occasionally be demonstrated. The evidence of a dyskeratotic process is quite constant. The changes in the corium are most varied, but signs of an inflammatory process are always present. There is an infiltration of lymphocytes, polymorphs and plasma cells in the pars papillaris of the derma. I have never been able to demonstrate distinctive changes in the elastic fibers. Any liquification necrosis that may be present seems confined to the basal-cell layer of the epidermis.

My aims in the therapy of postmenopausal pruritus vulvae are well expressed by the Latin tag *noli me tangere*. Avoid irritating an already irritated and infected skin. This is accomplished by directing the patient to keep the affected area constantly covered with a thick coating of bland ointment. A base of petrolatum alba with 20 per cent starch and thirty per cent zinc oxide is an ideal preparation. This crème is kept on the vulva for the minimum of three weeks, and the patient may cover it with squares of gauze to protect her clothing. As the

salve wears off, more is added. The patient may bathe as often as she desires, but she is not to attempt to clean off the salve. After her bath, she replaces the ointment washed away.

It is inadvisable to incorporate antipruritics in the salve. While they may afford temporary relief, they soon become ineffective, and all of them are irritants to some degree. In my experience, oil of cade, phenol, menthol, resorcin, calmine and the coal tar products eventually aggravate the pruritus.



Fig. 6.—A 62-year-old woman with pruritus vulvae. Macroscopically, a typical case of leucoplakia. There is evidence of hyperkeratosis and acanthosis. A broad zone of inflammation runs through the entire derma.

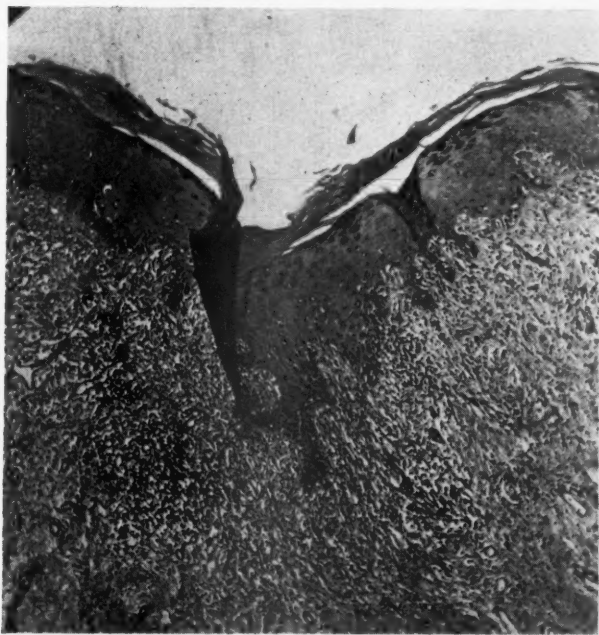


Fig. 7.—Posttherapy section after a complete clinical cure. There is still evidence of dyskeratosis. There is no longer a continuous zone of inflammation in the derma. There are focal areas of increased cellular density. High power examination reveals the cellular elements to be connective tissue. There are no neutrophils and only an occasional lymphocyte.

The constant application of the bland ointment protects the vulval tissues from all irritants and gives them the opportunity of coping with the dermal infection. Scratching is reduced considerably, since it is now mechanically unsatisfactory. After three weeks, as the pruritus abates, one may restrict the use of the ointment to nights only. The crème may be removed in the daytime, but the cleansing process must be accomplished by the use of cottonseed oil, mineral oil or salad oil. Soap and water may not be used for this purpose since this combination is irritating and requires too much rubbing.

In addition to this simple method of protecting the skin from infection and irritation, one must direct attention toward combating the extreme effects of atrophy of the external genitalia. In other words, we should attempt to increase the resistance of the skin besides protecting it from harm.

I recommend the use of large doses of vitamin A in the form of concentrated fish oils. The experimental skin lesions resulting from deficient vitamin A diets exhibit a type of hyperkeratosis and dyskeratosis which is similar to that found in pruritus vulvae.¹⁴ One must recall that vitamin A has been demonstrated to possess the ability of increasing the body's resistance to infections. It is not my intention to proclaim vitamin A the "anti-infection" vitamin, but one cannot ignore its proved infection-resisting quality.¹⁵

In questioning these older women who suffer from pruritus vulvae, I have often noted how restricted is their diet. Many of them avoid the majority of the vitamin A rich foods. Furthermore, the absorption of vitamin A and carotene from the intestinal tract is dependent upon normal fat metabolism. Liver cirrhosis will further prevent the conversion of carotene into vitamin A and will interfere with body storage.¹⁶

While it is true that only a few milligrams of vitamin A are required to satisfy man's minimal daily requirements, the combination of restricted diets and poor absorption can be responsible for an avitaminosis.

Attempts have been made to combat pruritus vulvae with estrogenic ointments.¹⁷ It is our experience that these preparations are unavailing in the treatment of postmenopausal pruritus vulvae. It has never been demonstrated that the estrogens have any effect on human skin, although we are all familiar with the responses of the vaginal mucous membrane to these hormones.

Estrogens used locally or systemically will cure senile vaginitis, but as we have already pointed out, senile vaginitis is rarely the cause of postmenopausal pruritus. In these older women, vaginal inflammations seldom develop a discharge profuse enough to flow out of the vagina and irritate the vulva.

It is claimed that estrogens will aid in combating atrophy of the external genitalia. This fact has not been substantiated by clinical results. One could scarcely expect the external genitalia to react to estrogenic therapy since the tissues usually are no longer capable of responding in a normal manner to the intrinsic ovarian steroids of the patient. A considerable percentage of postmenopausal women have a high estrogen level as can be proved by urine assays.¹⁸ Furthermore, cases of pruritus vulvae which exhibit atrophic and leucoplakic changes have been ob-

served in younger women who are menstruating regularly. Presumably their gonads are functioning normally, but the vulva has lost its ability to respond to the ovarian hormones.

Androgens, on the other hand, have proved effects on skin. Testosterone propionate stimulates the sebaceous glands and causes oiliness of the skin and hair. This hormone induces the sebaceous glands to secrete a soft, white, odoriferous material, and it has been reported that the vulval skin of castrated women participates in this secretory activity.¹⁹

It has also been demonstrated that androgens increase skin vascularization. Testosterone propionate dilates skin blood vessels, increases the blood's content of oxyhemoglobin, and stimulates the rate of blood flow.²⁰⁻²¹

With these skin reactions to the androgens in mind, we have used an androgenic ointment instead of our usual bland ointment in the treatment of those cases of pruritus vulvae where the outstanding macroscopic and histopathologic feature was atrophy. Observers familiar with the dry, thin, transparent skin of many of these cases, can readily appreciate the rationale of using a hormone which promises to stimulate the secretion of sebum and to increase skin vascularization.

In my hands, androgenic ointments have been successful in relieving pruritus vulvae. It is my impression that results are obtained more quickly with androgenic ointments than with the simple bland ointment in those cases which exhibit extreme grades of atrophy. However, I am not as yet prepared to state that my posttherapy biopsy material shows a qualitatively different picture after the use of the bland and the androgenic ointments. This picture, in cases which have been relieved of their pruritus, demonstrates the disappearance of the subepithelial inflammatory process. This infection by its very location must irritate the nerve terminations in the papillae of the derma, and in my opinion, it is the cause of all postmenopausal vulval pruritus.

Every biopsy we ever obtained from the vulval region of postmenopausal women complaining of pruritus vulvae clearly demonstrated an inflammatory process in the derma. All of our cases in which we obtained relief from the itching and were able to obtain posttherapy biopsy specimens showed a complete or almost complete disappearance of this infection. These findings were consistent regardless of the therapeutic regimen we employed.

I have been using a preparation containing 2 mg. of testosterone propionate to the gram of ointment.* It is employed exactly like the bland ointment. Since this hormone crème is expensive, it should be employed only where vulval atrophy is pronounced.

I believe that the use of the roentgen ray is not indicated in the treatment of postmenopausal pruritus vulvae. Clinical results are poor. Occasionally, temporary relief is obtained, but this is by no means the usual occurrence. In practically all instances, the pruritus is ultimately aggravated, probably because the atrophy of the genitalia is intensified by the action of the rays.

In my hands, the local injection of alcohol, as advocated by Wilson,²² has not been satisfactory. I have also injected histamine²³ and a com-

*Perandren Ointment supplied through the courtesy of Emile S. Fromer of the Ciba Pharmaceutical Products, Inc., Summit, N. J.

bination of procaine and benzyl alcohol in oil²⁴ without obtaining relief from itching. I have no experience with tattooing of the vulval skin,²⁵ but it seems to me that all these injection plans merely add insult to the already injured skin.

I have been able to secure pretherapy and posttherapy vulvar biopsies from fourteen cases of postmenopausal pruritus vulvae. The biopsies were all obtained from the inner surface of the left labia majora in the region of the clitoris, using local procaine anesthesia.

Although we have treated almost one hundred cases of postmenopausal pruritus vulvae during the past six years, we regard only these fourteen as complete studies. If biopsies are not obtained before and after the completion of therapy, it is not possible to truly evaluate the efficacy of any scheme of therapy. The subjective responses of the patient are a barrier to scientific clarity. Only too often have I suspected some of my older clinic patients of giving the investigator the answer they thought he wanted to obtain.

All of our fourteen cases were free of excessive vaginal discharge. None of them had diabetes, local parasites or specific skin diseases. All of them had the severest type of subjective symptoms. Every one had had previous therapy which ran the gamut from local applications and injections to parenteral hormonal therapy and x-ray exposures. The shortest period of observation since the final biopsy is now three months. The longest period is four years. Five cases of leucoplakia are included in this series.

We obtained satisfactory clinical results in all of these cases. The results ranged from perfect cures to cases where occasional recourse to ointment therapy as outlined here is necessary. I should like to be the first to point out that it is scarcely possible that any woman suffering from this complaint would submit to a posttherapy biopsy unless she had received satisfactory relief from her pruritus. This is the probable explanation of the almost perfect results recorded in those patients, who submitted to more than one vulval biopsy.

The posttherapy biopsies all show a marked diminution or complete disappearance of the inflammatory process in the pars papillaris of the derma. In the leucoplakic cases, dyskeratosis of the epithelium was still evident, but there no longer was any evidence of infection in the corium.

Summary

The theory is advanced that most cases of postmenopausal pruritus vulvae are basically due to a local atrophy of the skin. This permits an invasion and infection of the derma by the usual pathogenic skin organisms, which are always present in that region. The resulting inflammation affects the nerve terminations in the papillae of the derma and produces the itching. The macroscopic and microscopic pictures are largely determined by the individual's defense reactions. The same stimulus which will result in lichenification in one person will cause leucoplakia in another.

I believe that the best method of obtaining relief is to protect the skin from further irritation by the constant application of a bland ointment for at least three months.

An androgenic ointment should be used locally in those cases which exhibit severe vulval atrophy.

The successful treatment of fourteen cases of severe postmenopausal pruritus vulvae in which pretherapy and posttherapy vulval biopsies were obtained are reported. Five of these patients had leucoplakia of the vulva.

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PENICILLIN TREATMENT OF SULFONAMIDE-RESISTANT GONOCOCCAL INFECTIONS IN THE FEMALE*

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THE use of penicillin therapy in the control of gonococcal infections in the female has already been reported by several investigators.¹

A preliminary report on the successful penicillin treatment of sulfonamide-resistant gonococcal infections in 44 female patients under our care appeared in the *Journal of the American Medical Association* of April 8, 1944.² The present paper deals with the analysis of the ad-

*The laboratory work was aided by a grant from the United States Public Health Service.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

ditional results obtained in 108 hospitalized female patients suffering from gonococcal infections, who were treated with varying amounts of penicillin.

Clinical Material

A total of 108 adult female patients was diagnosed as gonococcus positive by cultures and/or smears during a 9-month period, from September, 1943, to June, 1944.

The urethra alone was found to be infected in 3 cases; the cervix alone in 39. A concurrent urethral and cervical infection was present in 66 women. Adnexal involvement was observed in 34 patients, although it was of a severe character only in exceptional cases. This paucity of acute adnexal disease may have been due to the long duration of the infection which averaged 70 days, and to the fact that the majority of the patients had already received two or more courses of sulfonamide in addition to other supportive therapy. One patient suffered from a diffuse peritonitis. Another developed arthritis of the right elbow during the course of penicillin treatment. Pregnancy ranging from 3 to 9 months was present in 6 patients.

Prior to penicillin treatment, 101 of these patients had failed to respond to at least two courses of 20 Gm. each of various chemotherapeutic agents of the sulfonamide group. The remaining 7 patients received penicillin treatment because they had shown a marked sensitivity to the sulfonamides.

Schedule of Treatment and Dosage

In order to determine a simple yet adequate schedule of penicillin treatment for sulfonamide-resistant gonococcal infections, the following plan was adopted: Two constant factors were maintained throughout the study: (1) A 3-hour interval between successive injections of penicillin, and (2) The intramuscular injection in the gluteal region.

The variable factors were: (1) the administration of varying amounts of penicillin, i.e., from 25,000 to 100,000 Oxford Units, as total dosage, and (2) the variation of the total period of time during which the total amount of penicillin was administered.

Three different brands of penicillin were investigated: Reichel Laboratories, Pennsylvania; E. R. Squibb & Sons, New York; Charles Pfizer, New York, but no essential differences of reactions or efficacy were observed. Each 5,000 Oxford Units of penicillin was dissolved in 1 c.c. of sterile normal saline.

The following table shows the number of hospitalized patients treated, the time required for each treatment, the amounts of single doses and the total dosages of penicillin, and finally the therapeutic results obtained.

Results of Therapy

All 108 patients treated with penicillin became bacteriologically negative with regard to cervical and urethral cultures. As may be seen in Table I, 99 patients who received varying amounts of penicillin over different periods of time, responded to a single course of therapy. The remaining 9 patients, who did not respond to the initial treatment, were cured by a second course of 100,000 O.U. given in divided doses of 25,000 O.U. each at 3-hour intervals.

TABLE I

| SCHEDULE NO. | NO. OF PATIENTS TREATED | NO. OF INTRAMUSCULAR INJECTIONS | HOURS REQUIRED FOR TREATMENT | OXFORD UNITS PER DOSE | TOTAL DOSAGE OF PENICILLIN O. U. | NO. OF PATIENTS | |
|--------------|-------------------------|---------------------------------|------------------------------|-----------------------|----------------------------------|-----------------|----------|
| | | | | | | CURES | FAILURES |
| I | 12 | 5 | 12 | 20,000 | 100,000 | 12 | — |
| II | 11 | 4 | 9 | 25,000 | 100,000 | 11 | — |
| III | 21 | 3 | 6 | 25,000 | 75,000 | 20 | 1 |
| IV | 15 | 2 | 3 | 25,000 | 50,000 | 12 | 3 |
| V | 29 | 2 | 3 | 50,000 | 100,000 | 28 | 1 |
| VI | 10 | 1 | 6 | 50,000 | 100,000 | 10 | — |
| VII | 1 | 2 | 3 | 25,000 | 75,000 | 1 | — |
| | | 1 | | 50,000 | | | |
| VIII | 1 | 3 | 6 | 20,000 | 60,000 | 1 | — |
| IX | 4 | 1 | — | 25,000 | 25,000 | 2 | 2 |
| X | 2 | 1 | — | 50,000 | 50,000 | 1 | 1 |
| XI | 2 | 1 | — | 75,000 | 75,000 | 1 | 1 |

Following penicillin treatment daily clinical and bacteriologic examinations of the hospitalized patients were performed. The patients were followed up for an average period of 7.8 days, during which an average of 5.7 examinations were carried out.

Reversal from positive to negative of the initial bacteriologic findings took place within 24 hours after termination of penicillin therapy in all but one case. In the one exception, reversal occurred after 48 hours. Among seven cases in which cultures were taken at hourly intervals after treatment had been initiated, three became negative within 2 hours.

The following factors seem to determine the therapeutic efficacy of penicillin in the treatment of sulfonamide-resistant gonococcal infections. (1) The administration of an optimal amount of penicillin: In this study, this amount proved to be a total dosage of 100,000 O.U. (2) The total period of time during which the total amount of penicillin was administered: 6, 9 and 12 hours were all found to be satisfactory. The intramuscular route of injection was used in all of these cases.

Some bacteriologic cures were obtained with amounts of penicillin smaller than 100,000 O.U. and administered in less than six hours. Single doses of 75,000 O.U., 50,000 O.U. or even 25,000 O.U. were likewise found to be adequate in some cases. However, this type of therapy is not to be recommended since the percentage of failures was high. The observation, that such subtherapeutic doses can cure individual patients, is consistent with laboratory findings that different gonococcus strains vary markedly in their susceptibility to penicillin.³

Clinical Changes

The following clinical changes were observed after penicillin therapy. The urethral discharge diminished in amount, or disappeared completely within a week or less in practically all of the cases studied. The cervical discharge, however, persisted in most cases throughout the entire follow-up period. In a very limited number of patients, the cervical discharge disappeared for a few days, but soon recurred. In general, it may be stated that the amount and character of the discharge observed in the urethra and cervix before and after penicillin treatment did not differ essentially from that observed in women receiving sulfonamide therapy.⁴

Adnexal Involvement

In 20 of the 34 patients in whom adnexal involvement was present, tenderness and thickening of the tubes or ovaries subsided within a few days after penicillin treatment. In 10 other patients suffering from acute exacerbation of chronic pelvic inflammatory disease, the acute symptoms and signs appeared to be improved by penicillin therapy. However, in these patients no essential changes were observed in the size or character of the adnexal masses which were present before therapy. In the remaining 3 cases, an exacerbation of the adnexal involvement was observed following the use of penicillin. One of the patients, without any adnexal disease prior to penicillin treatment, developed salpingitis following therapy. Within 1 to 2 weeks after penicillin treatment, the acute symptoms and signs of adnexal involvement disappeared in all 34 patients.

Gonococcal peritonitis, in the one patient reported, responded strikingly to 100,000 O.U. of penicillin; the same amount which was found necessary in less complicated cases. The patient who developed acute arthritis of the right elbow during the course of penicillin therapy recovered within a few days without any further treatment. The course of pregnancy in 6 patients was unaffected by penicillin.

There were 14 women who suffered from a concurrent infection of *Trichomonas vaginalis* which remained unchanged by penicillin therapy.

Clinical Follow-up

After their discharge from Bellevue Hospital, 81 of the total of 108 women were followed up at the Research Clinic of the Department of Health, City of New York, for an average period of 43.6 days during which an average of 3.5 examinations were performed. During the course of this follow-up, there were 15 women who were found to be gonococcus positive again after an average of 51.7 days and 3.4 examinations. Nine of these had originally suffered from adnexal involvement. The question arose as to whether these cases represented a relapse of their previous infection or new infections. Thirteen of the patients admitted new exposures, while 2 persistently denied the possibility of a new infection. Of these 15 women, 6 who were originally sulfonamide-resistant responded to one course of sulfathiazole therapy for their reinfection. Four, including the 2 who denied exposure, were cured by a second course of penicillin. The remaining 5 cases were delinquent.

It is difficult to decide whether these 15 cases represent instances of relapse or of reinfection. Among the hospitalized patients it was observed, that relapses after inadequate therapy always occurred within 24 hours after the administration of the penicillin. In the 15 women who became gonococcus positive during follow-up, reversals to positive occurred after an average of 51 days' observation. Thirteen of these admitted new exposures, the remaining two women were completely unreliable. Another fact which points to reinfection was that 6 patients in this group responded to one course of sulfonamides although they had previously been sulfonamide-resistant cases. In view of these facts, it is our impression that practically all 15 of these cases represent reinfections rather than recurrences.

Toxicity

One of the greatest advantages of penicillin therapy is the absence of any serious toxic symptoms in patients thus treated. The only complaint of the majority of these patients was a transitory numbness or pain following injection radiating from the site of injection in the gluteal region down to the thigh or ankle. Chills of a mild degree, rising temperature, a macular rash and generalized lymphadenopathy were observed in one patient, who suffered from a concurrent early syphilitic infection (Herxheimer reaction).

Comment

The total dosage of penicillin and the time-dose ratio are apparently the basic factors which determine a successful schedule of penicillin therapy. Our investigation was directed at evaluating the minimum effective dosage of penicillin due to the fact that the amount of penicillin available during the course of the study was very limited. Furthermore, we wanted to establish an effective time-dose ratio which could be used for the treatment of ambulatory patients. From our results thus far, it appears that a minimum total dosage of 100,000 O.U. of penicillin administered in 3 intramuscular injections at 3-hour intervals—an initial injection of 50,000 O.U. followed by 2 injections of 25,000 O.U. each—is a satisfactory treatment schedule which is completed within a period of 6 hours.

Although we have not yet encountered any instances of penicillin failure in our series, it is a possibility which cannot be eliminated at our present state of knowledge. Failure of penicillin might be due to two main factors: (1) A true resistance on part of the gonococcus strain to the bactericidal action of penicillin itself, the occurrence of which has not yet been proved; (2) the inability of penicillin to reach and act upon organisms which may be walled off in inaccessible foci of the genital tract.

It may be pointed out that a second course of penicillin treatment consisting of 4 single doses of 25,000 O.U. each, administered at 3-hour intervals has proved to be therapeutically effective in 9 patients who failed to respond to a first course of penicillin therapy.

The most difficult problem involved in this study of female gonorrhea is the establishment of definite cure. Clinical signs are of no appreciable value in its determination. Repeated bacteriologic examination, extended over a period of 2 to 3 months if possible, is the only means of establishing cure with any degree of certainty. The differentiation between relapse or reinfection after apparent cure is frequently impossible. History of new exposure, time of follow-up after treatment, number of examinations performed and final response or failure to a repetition of the original therapeutic schedule are factors which may aid in the clarification of this problem.

Summary and Conclusions

1. Various amounts of penicillin were used in the treatment of 108 adult female patients suffering from gonococcal infections. Of these, 101 had failed to respond to at least two courses of various sulfonamides; the remaining 7 patients showed a definite sensitivity to sulfonamide compounds.

2. Of the total of 108 patients, 99 promptly became bacteriologically negative after one course of penicillin treatment, and 9 by the administration of a second course of penicillin.

3. The results obtained by the administration of various amounts of penicillin point to the fact that a minimum total dosage of 100,000 O.U., injected intramuscularly in divided doses, is both necessary and sufficient for bacteriologic cure. The minimum total period of time required for successful therapy was found to be six hours.

4. Smaller doses of penicillin and shorter total time of treatment were adequate in individual cases, but this type of therapy cannot be recommended.

5. Urethral discharge following penicillin therapy disappeared within a week; cervical discharge was not appreciably affected in the majority of cases.

6. Acute symptoms and signs of adnexal involvement subsided within 1 to 2 weeks after penicillin treatment. There were 3 cases which had an exacerbation of the adnexal involvement immediately following the use of penicillin, and 1 patient who developed salpingitis following therapy.

7. After their discharge from the hospital, 81 of the total of 108 women were followed up for an average period of 43.6 days, during which an average of 3.5 examinations were performed.

8. Fifteen patients were found gonococcus positive after an average follow-up of 51.7 days. It may be assumed for various reasons that all these patients represent reinfections rather than recurrences.

9. No serious toxic symptoms appeared in this group of patients treated with penicillin.

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THE TRANSMISSION OF PENICILLIN THROUGH THE PLACENTA*

A Preliminary Report

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A STUDY was started in May, 1944, to determine what place penicillin might have in obstetric therapeutics. The first problem consisted of finding out whether or not the placenta would offer a barrier to the passage of penicillin from the maternal circulation into the fetal blood supply. If penicillin could be detected in the fetal blood, it seemed important to determine the amount necessary to give the mother in order to obtain an adequate therapeutic concentration in the fetus.

Procedure and Findings

Amorphous penicillin, as the sodium salt, was placed in solution with normal saline in concentration of 5,000 units per cubic centimeter. Labors were closely observed in order to give an intramuscular injection of penicillin to each patient within a period of less than two hours before delivery. At the time of delivery, penicillin blood levels were obtained both from the antecubital vein of the mother and the umbilical vein of the infant. In a few patients, in which delivery did not occur within the first hour after injection, maternal blood levels were obtained one hour after administration of the penicillin and at the time of delivery.

The bacteriostatic level of penicillin varies with different strains of organisms. The test strain used in this study was *Staphylococcus aureus* 209, for which the minimum bacteriostatic blood level has been determined to be 0.02 Florey units per cubic centimeter.^{1, 2}

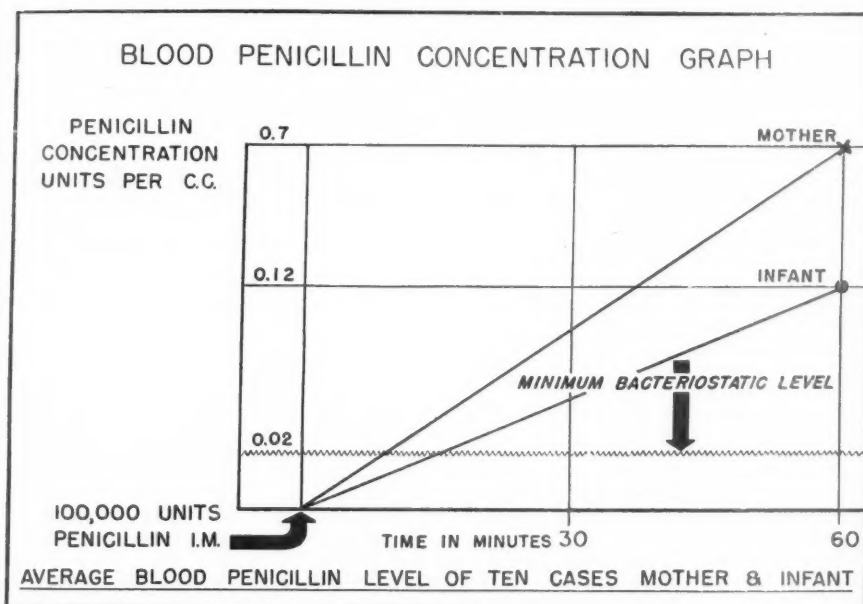
An initial dosage of 20,000 units was tried on one patient. Thirty minutes after intramuscular administration of penicillin to the mother, a penicillin level of less than 0.02 Florey units per c.c. was obtained from the infant cord. The maternal blood level at the time of delivery was 0.08 units per cubic centimeter.

Two patients were given 40,000 units of penicillin by intramuscular injections. Ineffective blood levels of less than 0.02 units per c.c. were obtained from the infants. The maternal levels were 0.08 units per cubic centimeter.

The dosage was then increased to a single 10 c.c. intramuscular injection of 100,000 units of penicillin (10,000 units per c.c.). With this dosage, observations were made on ten patients. Effective bacteriostatic levels were obtained in the fetal blood. The maternal levels ranged from 0.1 units per c.c. to 2.5 units per cubic centimeter. The fetal blood levels ranged from 0.02 units per c.c. to 0.2 units per cubic centimeter. A composite average of fetal and maternal penicillin blood levels is charted in Fig. 1. A complete record of maternal and fetal penicillin blood levels is given in Fig. 2.

*The opinions and views set forth are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

Fig. 1.



| PENICILLIN BLOOD LEVELS | | | | | | |
|-------------------------|---------|-------------------------------|--------------------------------|-----------------------------------|-------------------------------|--------------------------|
| PATIENT | DATE | | BLOOD LEVEL MOTHER 1ST. HR. | TIME INTERVAL BET. INJ. & DEL. | BLOOD LEVEL MOTHER AT DEL. | BLOOD LEVEL FOETUS |
| M.B. | 6-27-44 | PENICILLIN 100,000 UNITS I.M. | 0.3 $\frac{1}{2}$ c.c. | 1 hr. 45 min. | 0.1 $\frac{1}{2}$ c.c. | 0.06 $\frac{1}{2}$ c.c. |
| M.R. | 6-27 | | | 30 min. | 0.3 $\frac{1}{2}$ c.c. | 0.02 $\frac{1}{2}$ c.c. |
| W.M.S. | 6-27 | | | 55 min. | 0.6 $\frac{1}{2}$ c.c. | 0.1 $\frac{1}{2}$ c.c. |
| A.C. | 7-5 | | | 1 hr. 05 min. | 0.20 $\frac{1}{2}$ c.c. | 0.14 $\frac{1}{2}$ c.c. |
| K.P. | 7-6 | | 1.24 $\frac{1}{2}$ c.c. | 1 hr. 19 min. | 0.3 $\frac{1}{2}$ c.c. | 0.2 $\frac{1}{2}$ c.c. |
| R.B. | 7-11 | | | 1 hr. 17 min. | 0.4 $\frac{1}{2}$ c.c. | 0.14 $\frac{1}{2}$ c.c. |
| M.M. | 7-17 | | | 1 hr. 45 min. | 0.3 $\frac{1}{2}$ c.c. | 0.154 $\frac{1}{2}$ c.c. |
| G.T. | 7-18 | | | 58 min. | 0.62 $\frac{1}{2}$ c.c. | 0.14 $\frac{1}{2}$ c.c. |
| E.D. | 7-18 | | | 25 min. | 2.5 $\frac{1}{2}$ c.c. | 0.14 $\frac{1}{2}$ c.c. |
| A.J. | 7-18 | | | 1 hr. 06 min. | 1.2 $\frac{1}{2}$ c.c. | 0.14 $\frac{1}{2}$ c.c. |

Fig. 2.

Discussion

Our results confirm the report of Herrell, Nichols, and Heilman,³ that 100,000 units of penicillin injected intramuscularly into the pregnant patient at term will result in an adequate bacteriostatic penicillin level in the fetal circulation. We have no data on the passage of penicillin through the placenta of the patient in the first or second trimesters of pregnancy. One patient, K. P., had positive blood serology, but a normal appearing placenta. Another patient, R. B., had moderately severe pre-eclamptic toxemia with multiple small placental infarcts.

The fact that penicillin passes from the maternal into the fetal circulation in effective concentrations suggests a wide therapeutic application of a relatively nontoxic agent for the control of penicillin susceptible infections which affect the mother and her unborn infant. Of these infections, syphilis should receive greatest consideration. If penicillin will eradicate syphilitic infections in the mother and fetus, it should replace the much more toxic arsenical preparations in the treatment of syphilis in pregnancy. Penicillin, given during labor to patients with known gonococcal infections, should reduce the incidence of postpartum gonorrheal salpingitis and gonorrheal ophthalmia neonatorum. The prophylactic use of penicillin in patients with prolonged rupture of the membranes should reduce puerperal infection in the mother and increase fetal resistance to intrauterine pneumonia. It seems that the factor of safety for mother and infant would be increased by substituting penicillin for the more toxic sulfonamides in the treatment of all penicillin susceptible infections complicating pregnancy.

We wish to express our appreciation to Lieutenant P. V. Wolley, Jr. (MC), USNR, Bacteriologist of the National Naval Medical Center, Bethesda, Md., for determining the penicillin blood levels.

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THE ACTION OF VERATRONE ON BLOOD PRESSURE, URINE VOLUME AND UREA CLEARANCE IN THE TOXEMIAS OF PREGNANCY

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THE maintenance of normal kidney function in the toxemias of pregnancy is of utmost importance. Because the progression of pre-eclampsia is usually accompanied by a decrease in urinary output, many methods have been utilized in an attempt to promote the normal excretion of urine. At the present time, the administration of hypertonic glucose solutions to increase the blood volume through the withdrawal of extracellular water is the most effective method of accomplishing this purpose. There is no drug which may be used with any degree of success.

The positive water balance and the hypertension associated with pre-eclampsia and eclampsia are thought to be due, at least in part, to vascular spasm; thus, the use of a substance which will both lower blood pressure and relax the spastic vessels should be beneficial in the treatment of these conditions.

Veratrum viride was first used in the treatment of eclampsia by Barker about 1850; however, in the 1874 edition of his book *The Puerperal Diseases*, no mention of the drug is made except for its use in infections. Jewett, in 1887, reported a mortality rate of 27 per cent in 22 cases treated with veratrum, and Zinke¹ in 1911, was able to reduce his mortality rate from 34.4 per cent in 64 cases to 15.4 per cent in 26 cases by use of this preparation. Bryant² in 1935, reported a mortality of 10 per cent (121 cases), and in 1940,³ 1.7 per cent in 120 cases. In addition to veratrone, however, sedation, magnesium sulfate, glucose and induction of labor were liberally utilized.

Physiologic experimentation has revealed that the primary site of action is on the vagus center, stimulation of which is followed by slowing of the pulse and a fall in blood pressure, both being relieved by section of the vagi. Willson and Smith⁴ were able to demonstrate a direct peripheral vascular dilatation in animals. In these experiments, there occurred a drop in blood pressure without change in pulse rate and an increase in leg and spleen volume when the drug was injected into vagotomized dogs. The perfusion rate through isolated organs also increased when veratrone was injected into the perfusion system indicating that there is a direct dilating effect on the vessel wall.

Because little is known of the effects of this preparation on the vascular system in the human being, it seems desirable that its action be completely studied before its widespread use is again advocated. The results of the first of a series of studies on this problem are reported here.

Methods and Material

A total of 14 tests were made on prenatal patients, eight with essential hypertension, five with pre-eclampsia and one normal. Five of these subjects were again studied after delivery. All had been at complete bed rest for at least 24 hours prior to the test and all, except the normal, were on a pre-eclamptic diet (less than 2 Gm. of sodium chloride daily). Because of the constant oliguria or anuria associated with eclampsia, it was impossible to study this group.

Early on the morning of the test, the patients were given 200 c.c. of water by mouth; this was repeated at half-hour intervals and in all instances, a total of at least 1,600 c.c. of fluid was taken. A control urea clearance was begun at the end of the first hour, and at the completion of the control test, veratrone was administered subcutaneously, the initial dosages varying from 0.5 to 0.75 cubic centimeters. If after thirty minutes there had occurred no marked change in blood pressure another injection, usually 0.25 c.c., was given. The subsequent urea clearance periods were of at least 30 minutes' duration.

All urine specimens were collected by catheter at half-hour intervals, the bladder being emptied each time, and the amount carefully measured.

Results

Effect on Pulse Rate and Blood Pressure.—In most instances, the administration of the drug was followed by a reduction in pulse rate of at least 12 beats per minute (the lowest rate observed was 40) and a fall in blood pressure. In four cases, all with essential hypertension, the pulse rate either remained the same, or rose despite the fact that the blood pressure was decreased. Although the fall in blood pressure usually occurred coincidentally with the slowing of the pulse, this association was less apparent as the blood pressure returned to the preinjection level. In most instances, the pulse rate reached its original rate while the blood pressure remained low. No irregularities in heart action were observed. The depression of blood pressure was obtained more easily in the patients with pre-eclampsia than in those with essential

hypertension. In the former group, it was necessary to repeat the injection of veratrone only twice (40 per cent), while in the latter, subsequent dosages were necessary seven times (87 per cent) to produce a distinct fall in pressure. The maximum drop occurred in an average of two and one-half hours after the initial injection and was comparable for each group. The fall averaged 48/27 mm. Hg in those with hypertension, and 51/38 mm. Hg in those with pre-eclampsia from initial pressures averaging 168/115 for the former, and 163/116 for the latter.

The average time before the blood pressure returned to the control level exceeded six hours for all patients; in one patient with essential hypertension the blood pressure had not returned to the preinjection level in ten hours, and in one pre-eclamptic in 15 hours. The maximum drop was followed by a gradual rise to the control level.

More of the drug was necessary in the normal patient to effect an alteration in blood pressure than in the patients in whom the pressure was elevated. In this instance, after a total dosage of 1 c.c. of veratrone, there occurred a diminution from 130/80 to 100/60 mm. Hg with a return to normal within two hours after the most marked depression (Fig. 1).

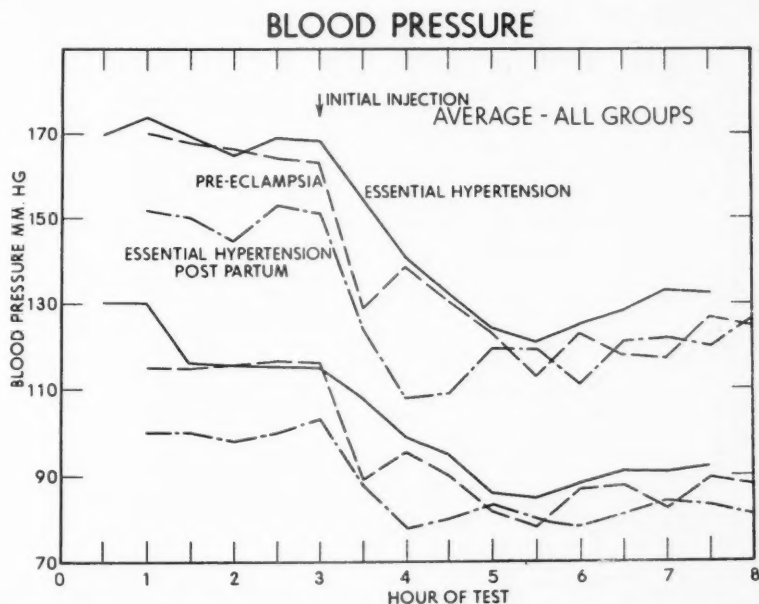


Fig. 1.—The effect of veratrone on blood pressure in pre-eclampsia and essential hypertension before delivery, and in essential hypertension during the postpartum period.

Effect on Urine Volume.—Although each patient ingested at least 1,200 c.c. of water during the control period, a definite difference in output was noted for the hypertensive patients as compared with those with pre-eclampsia. In seven of the former group, there occurred a gradual increase in urinary output during this period of hydration to a peak at the time of administration of the drug. The urine volume of the pre-eclamptic patients was altered only slightly by the administration of water by mouth. This observation is illustrative of one of the important differences in kidney function between the two conditions.

Following the injection of veratrone, a definite diminution in urine volume was noted in both groups; however, this change was much more marked in the patients with pre-eclampsia. In these subjects, the maximum depression occurred in 3½ hours when the volume per minute averaged only 4.3 per cent of that at the time the drug was given.

Of these five patients, all except one, had a urine output greater than 3 c.c. per minute during the control period. In each instance after

injection of the drug, this was decreased to less than 1 c.c. per minute for periods varying from 30 minutes to 4 hours. In four of the five patients, a complete suppression of urine occurred; of the latter one produced no urine for $\frac{1}{2}$ hour, two for one hour, and one for two hours.

The most marked depression of kidney function in the subjects with essential hypertension was noted two hours after the injection, at which time the output averaged 47 per cent of the control level. In only four patients was the urine output decreased below 1 c.c. per minute; two for 30 minutes; one for one hour, and one for $1\frac{1}{2}$ hours. In only one did urine excretion cease completely, the anuria lasting only $\frac{1}{2}$ hour. In the normal patient, the urine volume decreased to less than 1 c.c. per minute in one thirty-minute period during the most marked depression of blood pressure (Fig. 2).

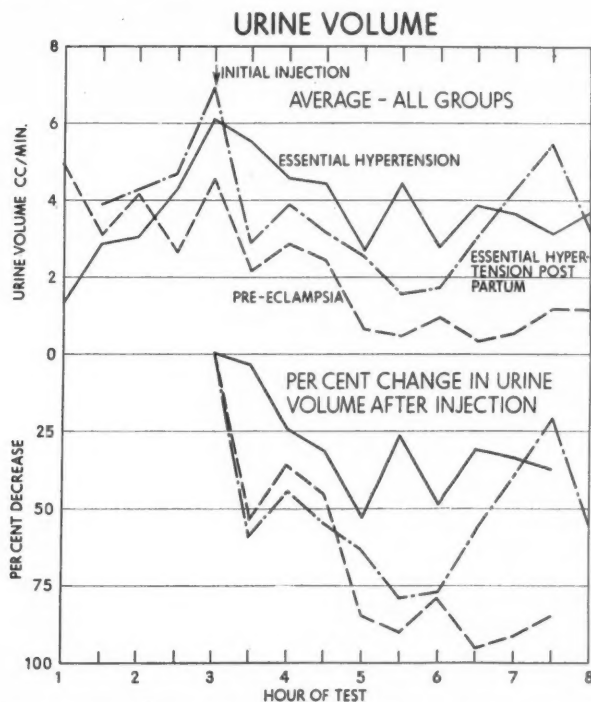


Fig. 2.—Effect of veratrone on urine volume. The upper chart shows the average urine outputs in c.c./min. for the three groups. The lower chart shows the percentage reduction in urine volume as a result of the injection of veratrone. The average urine volume in c.c./min. for the last half hour of the control period was taken as the base line and the reduction calculated from this figure.

Effect on the Excretion of Urea.—The administration of veratrone was followed by a definite reduction in urea clearance. This reduction appeared to be directly related to the diminution in blood pressure, since it became progressively more pronounced as the latter decreased, and improved with the return of the pressure to the original level. For the patients with pre-eclampsia (Figs. 3 and 4) the urea clearance just preceding the injection averaged 41 c.c. of blood cleared per minute; this was reduced in $2\frac{1}{2}$ hours to a minimum of 5 c.c. per minute. The clearance remained below 20 c.c. per minute for a total of two hours. Although subsequent urine volumes were not greatly increased, there occurred a rise in the urea clearance starting three hours after the drug had been given to an average of 35 c.c. per minute two hours later.

The decrease in urea clearance also was noted in the hypertensive patients (Figs. 3 and 4) but with the exception of one-half-hour period, was much less marked. The control clearance of 53 c.c. per minute was reduced to a low of 11 c.c. per minute in $2\frac{1}{2}$ hours; however, in direct

contrast to the pre-eclamptic patients, the preceding and succeeding figures were 33 and 34 c.c. per minute, respectively. During the period at which the clearance was at its lowest, the urine output was only 26 per cent below the control level.

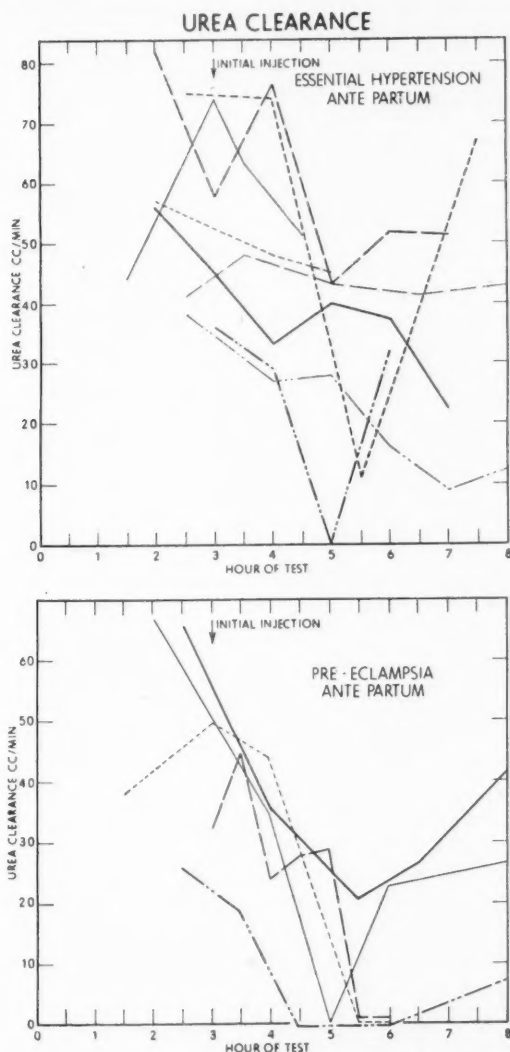


Fig. 3.—Effect of veratrone on urea clearance. The two charts showing the alteration in urea clearance in individual cases show the more marked drop in excretion in pre-eclampsia as compared with essential hypertension.

No significant alteration occurred in the normal patient.

In the hypertensive patients the figure for $U/B \left(\frac{\text{urine urea nitrogen}}{\text{blood urea nitrogen}} \right)$ fell as the urine volume increased during the period of hydration. No significant alteration in this figure followed the injection of veratrone. Little change in U/B was observed during the control period in the pre-eclamptic patients, probably directly correlated with the failure of increased fluid intake to alter markedly the urine output. Following the injection, this figure fell to 0 in those patients in whom the urine output was completely depressed; two rose above the control level with recovery of function, one from an initial figure of 10 to 24, and one from 15 to 38. In the others, no great change was noted.

Effect of Delivery.—The postpartum response to veratrone in a patient who had had pre-eclampsia was essentially the same as that during the

pregnancy. Although the control urine volume was higher after delivery, there occurred a pronounced diminution in output in response to injection of the drug; *complete suppression was not obtained despite the fact that the lowest blood pressure in the postpartum test was below that produced during the previous examination.* In this same patient, a period of urinary suppression lasting two hours had been precipitated by the drug during pregnancy.

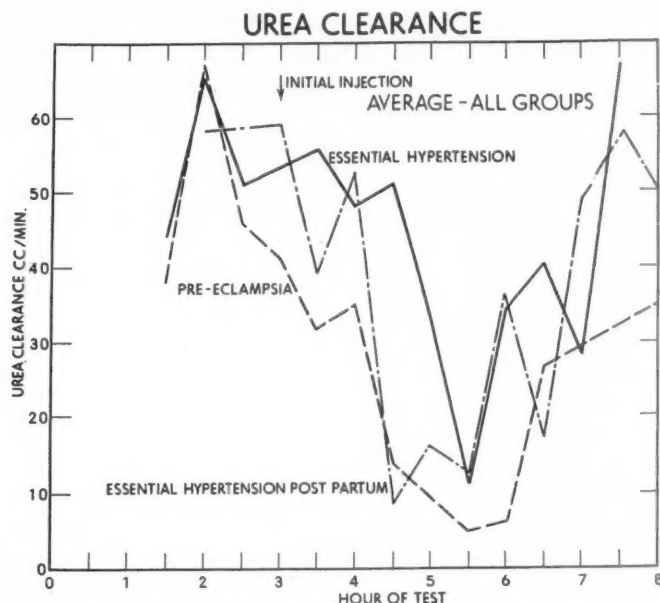


Fig. 4.—Average fall in urea clearance in pre-eclampsia and essential hypertension before delivery, and in essential hypertension during the postpartum period as a result of injection of veratrone.

The postpartum results in four patients with essential hypertension differed from those before delivery. The blood pressure drop averaged 44/25 mm. Hg and was noted one hour after the drug had been given. The average diminution in urine volume was greater than that of the hypertensive patients before delivery, but less than the figures obtained for those with pre-eclampsia. No subject failed to excrete urine even during the most marked depression of blood pressure. Recovery of kidney function occurred more rapidly after delivery than in either of the groups during pregnancy. The urea clearance decreased rapidly to its lowest point 1½ hours after the drug had been injected, and remained below 20 c.c. per minute for 1½ hours, an hour longer than the hypertensive patients during pregnancy. Little change was observed in the U/B.

General Reactions.—Most patients complained of burning at the site of the injection, but no marked local reaction developed in any case. Burning in the throat likewise occurred frequently. Four of the five pre-eclamptics vomited when the blood pressure dropped, but in only one of the hypertensive patients did this occur.

Discussion

Improvement during the course of pre-eclampsia only follows restoration of normal kidney function, and in the severe cases, this may be difficult or impossible to accomplish before delivery. Mere reduction of blood pressure is relatively unimportant in promoting the desired effect, since postpartum diuresis usually is established while the blood pressure remains elevated. It has been shown by McGee⁵ that when

intravenous sodium amytal is used to control eclamptic convulsions, hypotension and anuria may result. That the latter is a result of lowering of blood pressure is demonstrated by the fact that kidney function may be re-established following the injection of ephedrine to increase arterial tension. Warthin and Thomas⁶ were able to reduce both blood pressure and renal blood flow in hypertensive dogs by the intraperitoneal injection of pentobarbital.

Because of the constant association of vascular spasm with pre-eclampsia, it seems likely that the changes which occur may be at least in part, a result of the diminution in caliber of the vessels. That there are no permanent changes in the vessel walls, is suggested by the fact that recovery from pre-eclampsia is complete without demonstrable alteration in the cardiovascular system. A drug which relieves vessel spasm should be of value as an addition to the treatment of this condition. The observations reported here demonstrate without question that veratrone reduces the blood pressure in toxemic patients, and we know from animal experiments, that there is a direct vasodilating effect. The direct action on blood vessels without interference from the vagus cannot be measured in the normal human being; however, the fact that the return of the pulse rate to its original level was not necessarily accompanied by an elevation in blood pressure, suggests that there is a vascular effect other than that through the vagus nerves. In spite of the fact that the blood pressure was depressed to normal levels and that vascular spasm was reduced, the kidney function was not only unimproved, but usually was decreased to a dangerously low point. Thus, we may conclude that vascular spasm and hypertension alone are not responsible for the functional changes associated with pre-eclampsia.

The differences in response to the administration of veratrone in the patients with essential hypertension as compared to those with pre-eclampsia may be explained by differences in the vessel walls. In both pre-eclampsia and early essential hypertension, the changes are the result of vascular spasm, but in the latter group, there occurs a progressive structural alteration in the blood vessel walls. Vascular dilatation and a fall in blood pressure in pre-eclampsia are easily obtained because of the lack of organic change, and the same holds true for early essential hypertension. In the latter group as the vascular sclerosis increases, complete relaxation of the vessel walls becomes more difficult to achieve and the response is less marked.

The excretion of both water and solids by the kidney is dependent upon normal blood flow through the renal vessels, normal glomerular filtration and normal tubular reabsorption. Alteration in any of these factors may be reflected either in a change in volume of urine excreted, or in its chemical content. Although the fall in blood pressure in the cases studied did not reach levels low enough to suppress kidney function in normal individuals, the direct association of decreased urinary output with decreased blood pressure makes this factor seem the most likely cause. In one patient with pre-eclampsia, however, a small initial dose of veratrone depressed the blood pressure only to 130/90 from 160/110, but the urine volume decreased about 50 per cent. Complete study of glomerular filtration and renal blood flow before and after ad-

ministration of veratrone is necessary before the exact mechanism by which the depression of renal function is produced can be determined.

Conclusions

1. The effects of the administration of veratrone to patients with both pre-eclampsia and essential hypertension during pregnancy and after delivery were studied.
2. The administration of the drug was followed by a decrease in pulse rate and a marked fall in blood pressure. This response was obtained more readily in the patients with pre-eclampsia than in those with essential hypertension.
3. Coincidental with the fall in blood pressure, there occurred a diminution both in urine volume and in urea clearance which likewise was more marked in pre-eclampsia.
4. The changes in kidney function are probably the combined result of the fall in blood pressure and an alteration in renal vascular dynamics.

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THIAMIN STATUS DURING PREGNANCY

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THERE is evidence that the thiamin status of an individual can be determined by measuring the twenty-four-hour output of thiamin in the urine.¹⁻³ This finding is dependent upon the fact that when the individual takes approximately the same diet day after day, there is a consistent urinary excretion of thiamin. Melnick³ has shown that if a normal adult consumes a well-balanced diet including 860 micrograms of thiamin daily, the average 24-hour urinary excretion of thiamin will be 200 micrograms. In contrast to this good thiamin status when taking a normal diet, he shows further that, when an inadequate diet of 260 micrograms thiamin intake daily is continued for 23 days, the 24-hour urinary excretion fell to 25 micrograms. Similar information regarding the thiamin status can be obtained by giving a test dose of thiamin by mouth or parenterally, and measuring the amount of thiamin later excreted in the urine during a specified time. A third method for finding the thiamin status is to establish excretion peaks as carried out by Lockhart.⁴ By this method the basal excretion of thiamin is first

established for an eleven-hour period. The following day, a test dose of thiamin is given. On successive nights, these doses are progressively increased until the urine analysis shows that the excretion peak is passed. The excretion peak is the point at which the highest proportion of the administered thiamin is excreted.

The first method as afore-mentioned was used for this report and presents the urinary excretion values of thiamin chloride in normal pregnant women. Twenty-four-hour urine specimens were collected from two groups of patients. The first group served as controls and took no extra thiamin in addition to the diet, while the second group took daily additions of thiamin chloride by mouth. The amounts of thiamin added varied from 0.75 mg. to 1.5 mg. daily as indicated in Table I. These patients were seen in private practice throughout pregnancy and consumed a well-balanced diet including milk, cheese, eggs, meat, 2 leafy vegetables daily, fruits and cereals. All the patients studied gave birth to normal, well-developed and well-nourished infants with the exception of one twin pregnancy, in which case, the first twin was stillborn. The blood pressure readings and the routine urine examinations showed no abnormal findings. The total number of patients studied and here reported was 42, twenty-nine of whom were primiparas. On these patients 154 separate tests for thiamin excretion were carried out.

Technique of Procedure

All patients were given written as well as verbal instructions for the collection of the 24-hour urine specimens. The specimen was accumulated in a previously prepared gallon bottle containing 20 c.c. of 10 per cent sulfuric acid, thoroughly mixed and measured. An aliquot portion was then sent to the Maternity Hospital Laboratory, Cleveland, Ohio, for the thiamin determination. The determinations were made by the fluorescent method as described by Wang and Harris,⁵ in which the thiamin is oxidized by potassium ferrieyanide in an alkaline solution to thiochrome and read in the light of a mercury lamp under a suitable filter. Standards were prepared by adding known amounts of thiamin, oxidized to thiochrome, to blanks prepared from each urine sample. A number of precautions suggested by Dr. C. A. Mills⁶ was observed, especially that of using only Pyrex glass throughout, and redistilling all the reagents. Recoveries were determined with each specimen by adding small amounts of thiamin to portions of the original urines.

In Table I, are listed two groups of normal pregnant patients. Group I serves as a control since no extra thiamin chloride was added to the diet, while Group II includes the patients that took a specified amount of thiamin daily throughout the period of gestation. The average urinary excretion value of thiamin for each group is presented for each trimester of pregnancy. In the Control Group the results indicate a tendency for the excretion of thiamin to decrease toward the end of pregnancy. In other words, as pregnancy advances the demand for thiamin increases, and this finding coincides with the conclusion of Lockhart⁴ who used excretion peaks following test doses of thiamin.

In Table II, are listed two cases which demonstrate that multiple pregnancy or prolonged vomiting lead to a diminution in the urinary excretion of thiamin chloride. In the first case, the need for thiamin chloride is greater than in single pregnancies, while in the second case, the dietary intake of thiamin is lowered by the vomiting and this in turn leads to lowered excretion.

TABLE I.—AVERAGE 24-HOUR URINARY EXCRETION OF THIAMIN CHLORIDE IN
NORMAL PREGNANCY
MEANS—WITH STANDARD ERRORS—GIVEN IN MICROGRAMS

| | NO. PA- TIENTS | NO. TESTS | 1ST TRI- MESTER | 2ND TRI- MESTER | 3RD TRI- MESTER |
|--------------------------------------|----------------------|--------------|-----------------------|-----------------------|-----------------------|
| Group I | 8 | 12 | 286 ± 37 | | |
| Normal diet — no thiamin added | 10 | 24 | | 263 ± 25 | |
| | 10 | 17 | | | 249 ± 41 |
| Group II | 4 | 4 | 478 | | |
| Normal diet + 0.75 mg. thiamin daily | 16 | 41 | | 620 ± 44 | |
| | 17 | 39 | | | 483 ± 27 |
| Normal diet + 1.50 mg. thiamin daily | 0 | 0 | ----- | | |
| | 4 | 8 | | 932 ± 139 | |
| | 3 | 4 | | | 1131 |

TABLE II.—AVERAGE 24-HOUR URINARY EXCRETION OF THIAMIN CHLORIDE IN
MULTIPLE PREGNANCY AND PROLONGED VOMITING
MEANS GIVEN IN MICROGRAMS

| | PA- TIENTS | NO. TESTS | 1ST TRI- MESTER | 2ND TRI- MESTER | 3RD TRI- MESTER |
|---------------------------------------|---------------|--------------|-----------------------|-----------------------|-----------------------|
| Twin Pregnancy | B.R. | 0 | ----- | | |
| *Normal diet + 0.75 mg. thiamin daily | B.R. | 1 | | 270 | |
| | B.R. | 1 | | | 335 |
| Prolonged vomiting | J.C. | 1 | 473 | | |
| *Normal diet + 1.50 mg. thiamin daily | J.C. | 2 | | 516 | |
| | J.C. | 0 | | | ----- |

*Normal in quality, intake varied with conditions of patients.

Comment

Although the total number of patients studied is not large, yet two facts are evident and worth emphasizing. First in importance is the finding that a well-balanced diet does give the normal pregnant women a good thiamin status. In the Control Group of patients in which no thiamin was added to the diet, the average excretion of thiamin for each trimester was well over 200 micrograms, which Melnick³ gives as the amount of thiamin excreted on a normal diet. If thiamin is added daily in addition to the diet, the 24-hour urinary excretion is increased accordingly. For example, the small addition of 0.75 mg. daily approximately doubled the urinary excretion of thiamin over that of the controls. Therefore, excessive doses of thiamin to normal pregnant patients who eat a well-balanced diet are not justified.

In this connection it is well to remember that the requirement for thiamin is increased during normal pregnancy. Hoffman⁷ pointed out in 1924, that in his experience in Canton, China, beriberi developed more frequently in women during pregnancy than at other times. Also that beriberi tends to recur with recurring pregnancies. The recommendation of the National Research Council⁸ is that the diet should contain 1.8 mg. thiamin daily during pregnancy. Although the diets taken in this present experiment were not analyzed for thiamin content, yet the urinary excretion shows good thiamin status from diet alone.

The second fact that this report shows is that multiple pregnancy or prolonged vomiting lowers the urinary excretion of thiamin. In

Table II, the patient, B.R., who had a twin pregnancy, took a daily addition of 0.75 mg. thiamin. During the second and third trimesters, the 24-hour urinary excretion of thiamin was only 270 and 335 micrograms, respectively, while the normal, single pregnancy patients, who took the same daily addition of thiamin showed an excretion of 619 micrograms for the second trimester, and 483 micrograms for the third. Thus, this case of twin pregnancy showed a definitely diminished excretion of urinary thiamin in 24 hours. The second patient listed in Table II, J.C., continued to vomit 2 or 3 times a day from the sixth week through the first trimester of her gestation. Although she took a daily oral dose of 1.5 mg. of thiamin, the urine test for thiamin at the end of the first trimester revealed only 473 micrograms. Soon after this test the vomiting subsided, but the appetite remained poor and a second test done during the second trimester revealed that the thiamin excreted was 330 micrograms. The group of normal pregnant patients, who took a similar daily dose of thiamin, showed an excretion for the same period, i.e., the second trimester, of 932 micrograms. Therefore, in multiple pregnancy or prolonged vomiting, moderate daily doses of thiamin are not only justified but probably necessary, if a good thiamin status is to be maintained. The vitamin B intake could be increased easily by taking special high vitamin B bread as reported by Free⁹ in 1940.

Dexter and Weiss¹⁰ state that in toxemia of pregnancy, so far as we know today, the vitamin requirement increases no more than in normal pregnancy. Nixon¹¹ in 1942, however, found that in eclampsia the amount of B₁ excreted in the urine is significantly lower than in normal pregnancy, also the concentration of thiamin in the placenta was significantly below that of the placenta from normal cases. Siddall¹² in 1938, suggested a possible etiological relationship between vitamin B deficiencies and pre-eclampsia and eclampsia. In this connection, King's¹³ report from Hongkong in 1941 is significant. He observed 42 cases of eclampsia, 19 (45 per cent) of which were complicated by avitaminosis B₁. Of 13 deaths, 11 had this complication. Thus, in 85 per cent of eclampsia deaths, there was the double lesion of eclampsia and avitaminosis B₁. Missett¹⁴ observed that the incidence of late toxemia is definitely increased in cases having nausea and some vomiting in the first trimester; 41 per cent of multiparas and 51 per cent of primiparas, who experienced this form of early toxemia, being toxic in the last trimester. He also found that those who had moderately severe vomiting during the early months were even more liable to late toxemia. The incidence was 56 per cent of multiparas, and 57 per cent of primiparas. Therefore, he suggests the likelihood that the occurrence of late toxemia is indeed proportional to the severity of its early manifestations. Thus, in the vomiting of pregnancy great care should be exercised to maintain a good thiamin status, and parenteral injections of thiamin may be necessary.

Summary

1. This report is a study of the thiamin status of normal pregnant women, as determined by measuring the 24-hour urinary excretion of thiamin chloride. Forty-two patients were observed, and 154 tests for thiamin excretion were made.

2. The control group took no daily additional thiamin chloride and the average 24-hour urinary excretion during pregnancy was as follows: first trimester, 286 micrograms, second trimester, 263 micrograms, and third trimester, 249 micrograms.

3. The daily addition to the diet of a small oral dose of thiamin, namely, 0.75 mg., approximately doubled the excretion value over the control group.

4. Lowered amounts of thiamin chloride in the urine may be caused by prolonged vomiting, poor appetite, or multiple pregnancy.

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CARCINOMA OF THE OVARY TREATED PREOPERATIVELY WITH DEEP X-RAY*

Report of Three Cases

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THE treatment of cancer of the ovary is notoriously unsatisfactory. Probably less than 10 per cent of the solid infiltrating type and 40 per cent of the papillary adenocarcinomas survive five years. While the poor results are due in part to the tardiness in applying therapy, nevertheless, they have stimulated the search for improvement in the handling of these cases as we find them. Without exception, all who have studied the problem agree that in the treatment of carcinoma of the ovary, excision is the procedure of choice. Radiation for these cases is not so well established. Some support its use as an adjunct to operation, while others admit no benefit from radiation and assert that it can cause harm. This report of three inoperable cases of carcinoma of the ovary which were treated with deep x-ray therapy and were later found to be operable is presented as evidence that x-ray treatment may, in some cases, affect the course of the disease.

It is difficult to accurately appraise the effects of radiation. It is apparent that there was some effect upon the growth; although no great amount of destruction was noted. The effect was sufficient, however, to permit the removal of the mass later on.

*Presented at a meeting of the New York Obstetrical Society, May 9, 1944.

Whether these cases are isolated curiosities, or whether similar effects might be more frequently obtained can only be determined by further experience. The prevailing practice in ovarian neoplasms is to operate, to remove as much of the mass as possible even though large residual carcinomatous masses are left in situ, and then to employ x-ray. The generally unsatisfactory results following this treatment might make justifiable the planning of the treatment of papillary growths when not removable along the lines employed in the cases reported here.

A study of previous experiences in the use of radiation, follows along two lines, the statistical and the direct observation of individual cases. Statistical study is unsatisfactory mostly because of the great variation in standards of microscopic criteria, extent of disease, thoroughness of operation and follow-up interval.

Ford¹ found x-ray valuable after surgery and as a palliative measure when the condition was inoperable. Montgomery and Farrell² thought that radiation lessened pain and edema in addition to prolonging life. They reported the use of postoperative x-ray in 22 cases of ovarian cancer and found that all their cures were in the papilliferous type. They regarded it as important to consider the histologic diagnosis, grade of malignancy, degree of operability and radiation factors. Kean³ also favored postoperative x-ray. He found that it prolonged life and thought that it should be given even in hopeless cases as a palliative measure. Taylor and Greely⁴ reviewed the factors influencing end results in 138 cases of carcinoma of the ovary. They found that postoperative x-ray was especially useful in a limited number of the cases studied. Schmitz⁵ recommended x-ray postoperatively and suggested, that if the tumor was large and inoperable and ascites was present, the fluid be removed before deep x-ray was administered.

Harris and Payne⁶ in reporting 38 cases of carcinoma of the ovary found x-ray to be valuable as a postoperative measure. In addition, the following case, similar to the ones I am reporting, was cited: "An operation was begun, but the tumor was so far advanced that to continue the operation was thought inadvisable. A biopsy was taken which showed papillary cystadenocarcinoma of the ovary. The patient was given deep x-ray therapy, her condition seemed to improve and 33 months later she was operated upon again. At the time the report was given she had been well for five years."

Neither Lynch⁷ nor Meigs⁸ were enthusiastic regarding the use of radiotherapy in the treatment of carcinoma of the ovary. Goodall⁹, in a recent article, stated that cure or arrest of progress could not be expected from deep x-ray treatment alone, and that it occasionally caused harm by degeneration.

Deep x-ray as a preoperative measure is not a new procedure. Walthard and Heyman, as quoted by Geist¹⁰, have treated inoperable cases, which afterward became operable, with x-ray. In a series of 38 cases of carcinoma of the ovary, Marchetti¹¹ reported eight cases as having had an exploratory laparotomy and biopsy followed by roentgen therapy and a second operation. His conclusion was: "Unquestionably x-ray rendered operable a good part of previous inoperable cases in this group." Seven of these eight patients died with an average duration of life of seventeen months. One was alive twelve months after the second operation when the report was made.

Report of Cases

Three cases are presented in which the history and physical examination were comparable. In each instance, because of the size of the growth, density of adhesions, extent of infiltration and the apparently

hopeless outlook, the original operator did not remove the pelvic organs. A biopsy was taken and deep x-ray therapy was given which obviously caused the masses to become smaller and more movable and the implants on the peritoneum to shrink. Several months after the first operation, a second operation was performed in each case and at this time the neoplastic tissue and affected organs were removed. Two of the patients are still alive and apparently well after twelve and eight years. The third patient died of a carcinoma, thought to be unrelated, five years after the original operation.

CASE 1.—Mrs. E. S., Unit No. 348632, was admitted to Sloane Hospital for Women because of enlargement of the abdomen. She was operated upon on August 15, 1932. On opening the abdomen, it was found to contain a large quantity of straw-colored fluid and the pelvis and lower abdomen were filled with a granular, cauliflower-like mass the size of a six months' pregnancy. Numerous implants were noted on the parietal and visceral peritoneum,; the liver and epigastric regions were thought to be unaffected. As the condition was deemed inoperable, a biopsy was taken and the abdomen closed.

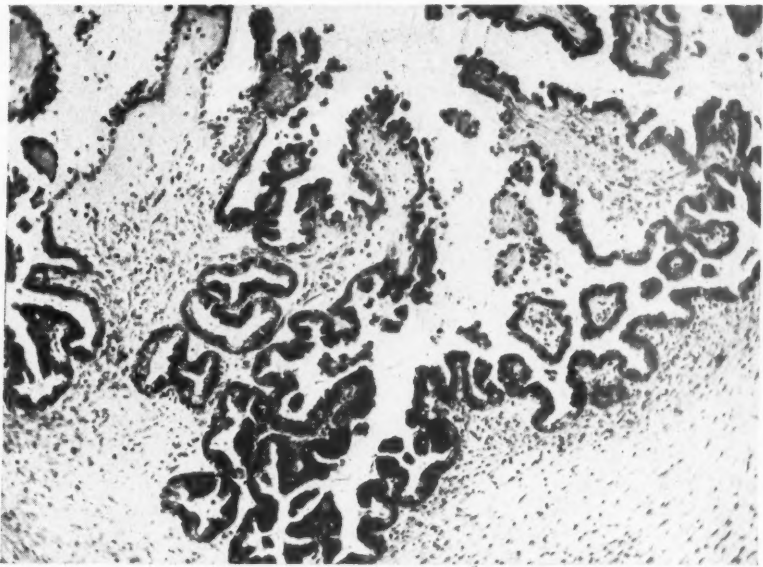


Fig. 1.—Sloane Hospital Pathology No. 6343 (Mrs. E. S.) shows microscopic disappearance of ovarian tumor tissue before radiation.

Microscopic Examination: (Fig. 1.) The epithelium in places was arranged in a single layer and was low cuboidal in type. In other places, many papillary folds were seen and the epithelium was high cylindrical in shape with basal nuclei. In some folds the cells were closely packed and formed irregular masses on the surface. The nuclei showed polymorphism varying in size, shape and staining quality. Many mitotic figures were visible. Numerous fibroblasts were seen in the supporting structure. Although the epithelium grew downward and in places formed alveolar-like spaces, the basement membrane was intact.

Diagnosis: Papillary cystadenocarcinoma of the ovary.

Deep x-ray therapy was instituted as a palliative and possible therapeutic measure. Between August 19, and September 16, 1932, inclusive, twenty-one exposures were given to the pelvic region through two fields, one anterior and one posterior, each measuring 20 cm. by 20 centimeters.

Each exposure was as follows: Kilovolts, 180, Anode skin distance

50 cm. Filter 0.55 mm. copper and 1.0 mm. aluminum. Total, 1,500 r. per field.

Also between December 28, 1932, and February 3, 1933, twenty exposures were given to the pelvic region through three fields, one anterior and two posterior each measuring 20 cm. by 25 centimeters.

Each exposure was as follows: Kilovolts, 180, Anode skin distance 50 cm. Filter 0.55 mm. copper and 1.0 mm. aluminum, Total, 1,700 r. per field.

The patient was examined in the Follow-up Clinic, one month after completing the second series of deep x-ray, the mass was thought to be smaller and more movable and a postoperative ventral hernia was noted. It was decided to perform another laparotomy with the hope that the tumor could be removed and the hernia repaired. On March 17, 1933, seven months after the first operation, a supravaginal hysterectomy and bilateral salpingo-oophorectomy were done. Upon opening the abdomen, the peritoneal implants were found to have entirely disappeared. A small amount of ascitic fluid was present and one whitish plaque was seen beneath the old scar. The pelvis and lower abdomen were filled with an irregular-shaped mass the size of a five months' pregnancy. There were a number of peritoneal adhesions in the pelvis. The uterus was normal in size. Both ovaries were cystic and in several areas papilliferous excrescences extended through the surface. In addition to cauliflower-like masses of tissue, some of the cysts contained a lemon-yellow thin fluid and others contained a thick brownish mucoid material. The right ovary measured 17.5 by 9.5 by 7 cm., and the left ovary measured 16 by 11 by 9 centimeters.

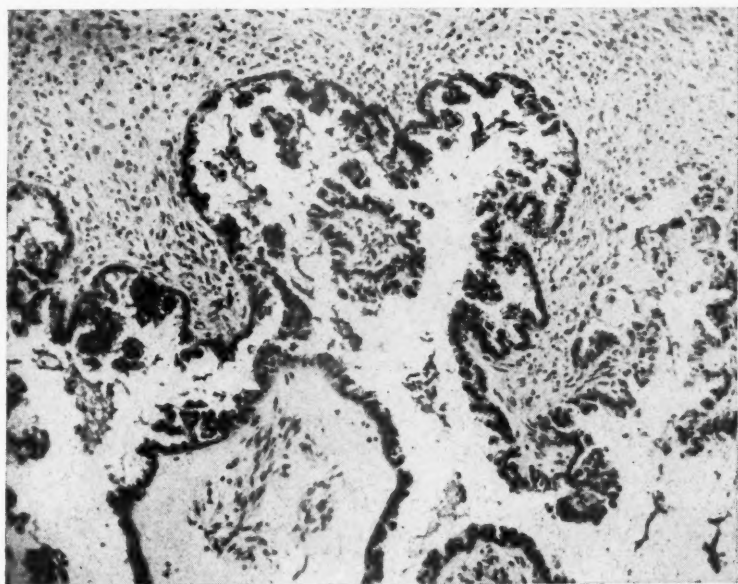


Fig. 2.—Sloane Hospital Pathology No. 6920 (Mrs. E. S.) shows microscopic appearance of ovarian tumor tissue after radiation.

Microscopic Examination: (Fig. 2.) The uterus was not remarkable except for the presence of an endometrial mucous polyp. In the serosa of both tubes, dilated lymph channels were seen which contained epithelial cells resembling the epithelium of the tumor masses. On the outer wall of the cyst were a number of papillary excrescences covered with tall atypical columnar epithelium. The nuclei varied in size, shape and staining quality. Some mitotic figures were seen. In some areas the basement membrane was absent and the underlying stroma was invaded by tumor cells. There were a few small masses of bluish-staining calcified material in several areas in the cyst wall. The epithelium lining the cyst was similar to that described on the outer wall.

Diagnosis: Endometrial polyp; atrophy of endometrium; atrophy of uterus,
The right tube showing lymphatic extension of growth,
Papillary cystadenocarcinoma, right ovary,
Left tube showing lymphatic extension of growth, and
Papillary cystadenocarcinoma, left ovary.

This patient had an uneventful convalescence and has remained well. The abdominal wall was firm and the pelvis was clear. It has now been eleven years after the first operation, and ten years since the second operation, and she was last seen in the Follow-up Tumor Clinic on October 8, 1943.

CASE 2.—Mrs. L., Unit No. 485440, a thirty-year-old married nulligravida, was admitted to the Presbyterian Hospital on April 24, 1936, with a history of having had fever and night sweats for six weeks. During most of this time, the abdomen was distended. For the past two weeks, she had had abdominal cramps. A diagnosis of tuberculous peritonitis or possibly an ovarian cyst was made, and on May 7, 1936, an exploratory celiotomy was done.

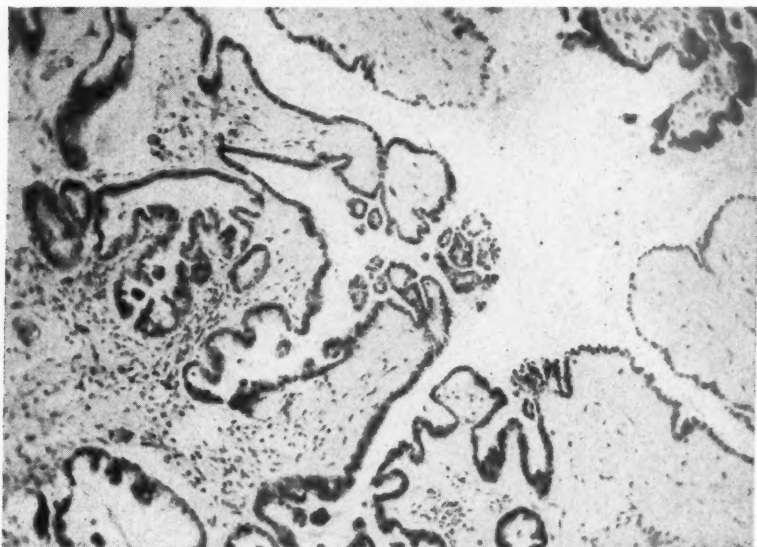


Fig. 3.—Presbyterian Hospital Pathology No. 60732 (Mrs. L.) shows microscopic appearance of ovarian tumor removed at primary operation before radiation.

The abdomen contained approximately 12 liters of straw-colored fluid. The upper abdomen seemed to be normal. The liver was smooth, the kidneys were of normal size and also the spleen. The small bowel was injected, but otherwise was normal. The pelvis was filled by a dense matted mass of adhesions and the individual structures could not be identified. Just beneath the bladder was a shelf of grayish-fibrinous tissue, which seemed to form a bridge across the pelvis and through this passed the sigmoid. The appendix was edematous and adherent to the shelf of tissue. Deep in the pelvis was a considerable quantity of friable grayish-white material resembling the implantations occurring with papillary carcinoma of the ovary. "Because it was apparent that nothing surgical could be done, we were satisfied with removing some pieces of this tissue for pathological examination and proceeded to close the wound."

Microscopic Examination: (Fig. 3.) The specimen was quite glandular. Cells varied in size and shape and staining quality, with vesicular nuclei which showed about three mitotic figures per high power field. The tumor was thought to be anaplastic.

Pathological Diagnosis: Papillary carcinoma of the ovary.

The postoperative course was uneventful and the patient left the hospital on the twenty-third day. The wound healed by primary union. Deep x-ray therapy was begun on the sixth postoperative day and apparently caused some nausea. Between May 13, and May 29, 1936, when the patient was discharged, fifteen exposures of deep x-ray were given to the pelvic region, through three fields, two anterior and one posterior, each measuring 10 cm. by 15 centimeters.

Each exposure was as follows: Kilovolts, 200, Anode skin distance, 50 cm., Filter, 1.0 mm. copper and 1.0 mm. aluminum, Total 1,050 r. for each anterior field and 150 r. for the posterior field.

This series was completed at the Queens General Hospital between June 4, and June 23, 1936: 1,050 r. were given to the posterior right and posterior left pelvis, 150 r. were given daily filtered with $\frac{1}{2}$ mm. of copper and 1.0 mm. aluminum. On admission to the Roentgenological Department of the Queens General Hospital, the patient appeared to be debilitated, and the entire pelvis was thought to be filled with a firm diffuse nontender mass. On June 21, 1936, the following notation was made, "Patient is now greatly improved. Her appetite is good. The ascites has entirely cleared. On vaginal examination, the pelvic mass was found to be considerably smaller and softer."



Fig. 4.—Sloane Hospital Pathology No. 10802 (Mrs. L.) shows microscopic appearance of ovarian tumor tissue after radiation.

On December 8, 1936, a laparotomy was performed at Sloane Hospital for Women. A moderate amount of clear fluid was present in the abdominal cavity. On both sides, in the region of the ovaries, were cystic masses of friable tissue approximately 8 cm. in diameter, which were adherent to the side wall of the pelvis and to the intestines, but did not involve the peritoneum, omentum or any other structures. Both tubes and ovaries were removed. The uterus was not removed.

Microscopic Examination: (Fig. 4.) Irregular papillary excrescences and partially hyalinized fibrous tissue suggestive of psammoma bodies were seen. The projections were covered for the most part with a single layer of columnar epithelium. In some areas, however, the cells were found to be grouped in several layers giving the appearance of pseudostratification. There was relatively little change in the size, shape and staining quality of the cells. Occasional mitotic figures were observed.

A diagnosis of papillary cystadenoma was made.

Convalescence was uneventful and the patient weighed 103½ pounds when discharged from the hospital. Stilbestrol was given for hot flushes. She attends the Tumor Clinic at regular intervals and when last seen on January 7, 1944, her weight was 138½ pounds, her general condition was good and her pelvis was clear. It has now been seven and one-half years since her first operation, and seven years since her second operation.

CASE 3.—Mrs. I. G. P., Unit No. 429174. A thirty-one-year-old nullipara was admitted to Sloan Hospital for Women because of abdominal swelling and discomfort of one month's duration. A diagnosis of tuberculous peritonitis or ovarian neoplasm was made, and on January 25, 1934, a laparotomy was done. A large amount of ascitic fluid was found, the peritoneum was injected and adhesions were present between the pelvic mass and the intestines. The pelvis was filled with a pinkish-white cauliflower growth which extended to the level of the umbilicus. It was felt that excision was not feasible and a biopsy was taken. Microscopic study showed that the tumor was a malignant papillary serous cystadenoma of the ovary. (Fig. 5.)



Fig. 5.—Sloane Hospital Pathology No. 8396 (Mrs. I. G. P.) shows microscopic appearance of ovarian tumor tissue before radiation.

On January 10, 1936, the patient was seen in the Tumor Follow-up Clinic. She was in a debilitated condition and had had numerous paracenteses for recurring ascites. She was remarkably free from symptoms except for abdominal discomfort due to tension when a paracentesis was needed. The abdominal mass was unchanged. In view of our experience with the two previous cases, it was decided to try x-ray therapy.

Between January 15, 1936 and July 8, 1936, fifty-eight exposures of deep x-ray were given, through four fields, two anterior and two posterior, each measuring 15 cm. by 15 centimeters.

Each exposure was as follows: Kilovolts, 190 to 200, anode skin distance 50 cm., filter 0.55 mm. copper and 1.0 mm. aluminum, total 1,600 r. for each of the anterior fields, and 1,000 r. for each of the posterior fields.

Following roentgen therapy, the abdominal mass was reduced in size. Improvement was noted in the patient's general condition, and there was less localized pain.

A second laparotomy was planned with the possibility of removing the pelvic growths. On December 11, 1936, the operation was per-

formed and large masses of glistening white cauliflower-like tissue were found extending halfway to the umbilicus. The tissue was soft and friable. The liver was smooth. A hysterectomy and bilateral salpingo-oophorectomy were performed and the diagnosis of carcinoma of the ovary was confirmed microscopically. (Fig. 6.) The operation was complicated by peritoneal adhesions which were probably due, at least in part, to the 85 paracenteses that were done in the two years prior to the operation.

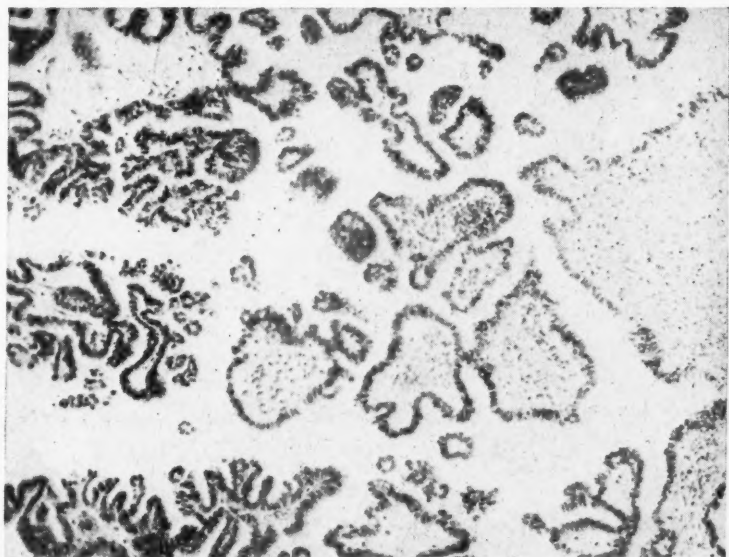


Fig. 6.—Sloane Hospital Pathology No. 10812 (Mrs. I. G. P.) shows microscopic appearance of ovarian tumor tissue after radiation.

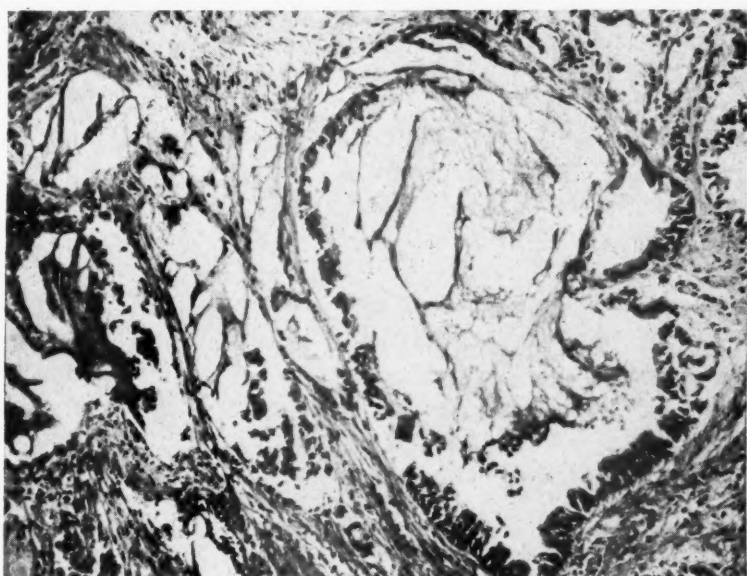


Fig. 7.—Presbyterian Hospital Autopsy No. 13028 (Mrs. I. G. P.) shows microscopic appearance of tumor of the intestine which resulted in perforation and death of the patient.

The postoperative course was satisfactory and the patient left the hospital on the sixteenth day. General improvement was noted and examination showed the abdomen firm and the pelvis clear. She resumed a normal life, came to the Follow-up Clinic at regular intervals, and did some work as a substitute public schoolteacher. In February,

1939, she was admitted as an emergency after a two weeks' illness, a diagnosis of intestinal obstruction was made and a cecostomy was done on February 27, 1939. The patient died shortly after the operation. Autopsy revealed no evidence of carcinoma of the ovary. The cause of death was perforated carcinoma of the colon.

Autopsy (No. 13028).—A. M. Pappenheimer: "Quite unexpectedly there was disclosed at autopsy a perforated adenocarcinoma of the sigmoid, located several inches above the site of the previous pelvic tumors; there was one small metastatic nodule in the pelvic tissue, but no distant metastases. The histological structure of the tumor of the colon (Fig. 7) is that of a colloid adenocarcinoma, which is unquestionably unrelated to the ovarian tumor. The regression of her ovarian tumors is complete, save in one portion of the remaining ovarian tissue in which there are still found a few papillary cysts lined by low, not actively growing epithelium, which may represent the remains of the original growth. There is not a trace of the previous peritoneal implantations. The case is instructive in demonstrating the possibility of curing what was probably a malignant epithelial tumor, and in showing that the regression of one epithelial neoplasm confers no immunity to the development of a new spontaneous carcinoma."

Discussion

The most interesting point in these cases is the clinical experience in three cases suffering with apparently inoperable ovarian tumors which were made operable by x-ray therapy.

Should these cases be called carcinoma? Grossly, they were definitely malignant. There was massive local extension to the pelvic wall and intestine and infiltration preventing separation of the growth from the surrounding structures and peritoneal implants. As in many ovarian neoplasms, the process was limited to the abdominal cavity. Microscopically, the evidence of malignancy was unsatisfactory as in most of the papillary growths of the ovary. Morphologically, there was only occasional evidence of rupture of the basal membrane and infiltration. Cytologically, there was some variation in the size and shape of the cells, some loss of polarity of the nucleus and slight increase in mitoses. On the whole, however, it would be impossible to classify any of the three neoplasms as definitely benign or definitely malignant.

The effects of the radiation are similarly apparent in gross rather than in microscopic changes. The size of the mass was reduced. It became localized. The most striking effect was the elimination of infiltration. This permitted the papillary process which still persisted to be separated easily from intestines and the parietal peritoneum. Isolated peritoneal implants also disappeared. Microscopically, there was a slight flattening of the cells and a return of the nuclei to the base of the cells.

Summary

1. Three cases of papillary cystadenocarcinoma, inoperable because of massive infiltration into the surrounding structures, are presented which were apparently made operable by deep x-ray therapy.
2. In all three cases the neoplasm was limited to the abdominal cavity.
3. The x-ray profoundly affected the gross appearance of the tumors, but caused very little change in the microscopic picture.

4. Two of the patients are alive after eight and twelve years, respectively; the third succumbed after five years of an apparently unrelated carcinoma.

Conclusions

1. Deep x-ray therapy in the three cases reported caused the papillary excrescences and transplants to shrink and the entire mass to diminish in size, thus making operation easier.

2. This study indicates that it is unwise to persist in doing a difficult primary operation. In some cases of massive infiltration, it may be safer to take a biopsy, close the abdomen, give deep x-ray and perform a second operation at a later time.

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47 EAST SIXTY-THIRD STREET

Discussion

DR. JAMES A. CORSCADEN.—I observed the original condition of two of the cases and all three at the secondary operation. Most dramatic was the change in the gross appearance. In all three cases the growth infiltrated the surrounding tissues, the pelvic wall and intestines. At the second operation, there were still masses of cauliflower tissue but they could be separated cleanly from the surrounding tissue.

The second point which interests me is the contrast between the gross appearance of these growths and the microscopic picture, one having every aspect of malignancy, the other showing few of the characteristics of an invasive carcinoma.

The practical application of the experience in these three cases would be that, in apparently hopeless, invasive cases, to carry out the procedure performed here,—the exploratory incision, the taking only of a biopsy and no attempt made to scoop out the removable material, the giving of adequate x-ray therapy and a second operation several months later. Certainly the partial removal of ovarian carcinoma and subsequent radiation has not given very satisfactory results. The other procedure would at least be worth trying.

GANGRENE OF AN EXTREMITY IN A NEWBORN CHILD

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THE following instance of gangrene of an extremity in a newborn infant is recorded in order to draw attention to an apparently rare fetal condition, of which, to date, only 42 cases seem to have been reported in the literature.

Case Report

A white multipara, 33 years of age, was first seen at the Hutchinson Memorial Clinic of the Tulane University of Louisiana School of Medicine April 13, 1938, in the tenth week of her eighth pregnancy. The last menstrual period had occurred February 7, and the estimated date of confinement was November 14, 1938.

The patient's seven previous pregnancies had been without incident and had terminated in spontaneous full-term deliveries. Inquiry into the personal and family history revealed nothing of significance. Physical examination revealed no abnormalities and the pelvic measurements were adequate. The blood serologic reaction was negative and all other laboratory data were within the normal range of values.

The pregnancy progressed uneventfully. Fetal movements were felt early in July. The initial blood pressure was 115/80 and the highest pressure, 130/90, was observed September 22. The patient weighed 147 pounds on her first visit to the clinic, and 177 pounds October 11, 1938.

The following day the membranes ruptured and a large amount of water was lost. No pelvic examination was made at this time. When labor had not ensued at the end of 48 hours, medical induction was carried out by the use of castor oil followed by a hot enema. Pains occurred promptly, and pelvic examination an hour later showed the cervix fully dilated and entirely effaced. The presentation was vertex and the position L.O.A. The fetal heart tones were strong. After a 20-minute second stage a viable male child, weighing 10 pounds, was delivered spontaneously and without difficulty, except that as the head was delivered, the left hand was found to be prolapsed between the cranium and the bony pelvis.

The child cried promptly and was normal in all respects except that the skin was missing from, and a wide path of excoriation involving, the dorsal surface of the first phalanges of the second, third, fourth and fifth fingers. The remainder of the hand presented a normal pinkish hue and arterial pulsations in the extremity were of normal strength. The entire extremity, however, seemed incapable of active motion.

As the day progressed the child's respirations became rather shallow and the hand began to assume a bluish-red tinge. Sixteen hours after birth he was admitted to Touro Infirmary, at which time the following notes were made:

This is a full-term newborn male child, whose physical findings present no abnormalities except as follows:

The face is very red and slightly edematous. Respiration is rapid and shallow and inspiration is occasionally accompanied by a moan or grunt. There is dullness over a small area posteriorly at the level of the angle of the scapula, and subcrepitant râles are heard over the same area. The left arm lies limply by the baby's side; passive motion causes pain, and active motion seems impossible. The forearm and hand are slightly edematous. Across the dorsum of the first phalanx of the second, third, fourth and fifth fingers is a bright red excoriation about 1 cm. wide. The fingers and fingernails are blue, the color being deepest on the second and fourth fingers. A purplish discoloration extends up the thumb

to the dorsum of the hand. Arterial pulsations are of normal strength. The whole extremity feels rather cool.

Spinal puncture revealed clear fluid under no increase in pressure. Examination of the fluid showed 30 white blood cells and many red blood cells per high power field. The globulin content was within normal range.

The child was assumed to have pneumonia and was placed on the routine pneumonia regimen, including the oxygen tent. Within 24 hours the lung findings were normal and it was concluded that they were due to pulmonary congestion rather than to pneumonia.

A surgical consultant believed that the condition of the left hand was caused by ecchymosis rather than by incipient gangrene, and advised conservative therapy, including heat and elevation of the extremity. For 48 hours slight improvement seemed to be occurring. The fingers remained dark and cool, but the extremity became warmer elsewhere, and the swelling disappeared. At the end of this period, however, definite progression occurred, and by the tenth day of life the distal two-thirds of all the digits, including the thumb, were clearly gangrenous and an irregular line of demarcation could be traced on the dorsum of the hand at the base of the fingers and on the volar aspect about the middle of the palm. The whole extremity was cold and arterial pulsations could not be felt.

Amputation of the forearm was carried out the following day, under drop ether anesthesia. A guillotine amputation just above the left wrist was attended with practically no bleeding, and reamputation was therefore done at the junction of the upper and middle third of the forearm, at which level the blood supply seemed entirely normal.

The pathologist reported as follows:

One specimen consists of an infant's left hand and 5 cm. of the distal portion of the forearm. All five fingers are involved in a gangrenous process which terminates grossly at the metacarpophalangeal articulation. There is some loss of skin over the palmar surface of the hand. The tissue is degenerated and gangrenous, and some of the blood vessels are distended, but definite thrombosis or other abnormalities cannot be demonstrated in any of the areas examined.

The other specimen, which consists of a portion of forearm, presents no abnormalities.

The child was not disturbed by the operation and continued to nourish well and gain weight. A rather extensive slough and wound infection in the stump required the removal of the sutures (interrupted dermal) on the fifth day, and the use of various local measures as well as injections of whole blood and ultraviolet therapy. The soft tissues of the axilla and about the shoulder joint were involved in an infectious myositis before the process was brought under control, but the child was in excellent condition and the wound was well healed when he was discharged from the hospital on the thirty-fourth postoperative day. At this time he had full motion of the stump.

Examination at the age of seven weeks in the Pediatrics Clinic of the Tulane University Hutchinson Memorial Clinic showed no abnormality except the absence of the upper left extremity. The gain in weight had been average for the duration of life. The blood serologic reaction was negative, and values for all blood elements were within normal range. The mother was carefully questioned at this time concerning possible abnormalities of pregnancy or parturition on either side of the family, but none was revealed.

The child continued to gain normally until the age of three months, at which time he developed bronchopneumonia, which proved fatal. Autopsy was not permitted.

Discussion

Gangrene of an extremity in the newborn infant is an apparently very rare occurrence. According to Heller and Alvary,¹ who made a

complete review of the literature and a tabulation of reported cases in 1941, there had been recorded to date 40 cases, including their own, of which nine, including their own, were instances of gangrene of the upper extremity, and of which five, including their own, were reported in the American literature. Their comprehensive study supplements Kosmak's² report in 1908, of one personal and four collected cases, and Dohan's³ report in 1934, of one personal and 25 reported cases.

Kosmak omitted several cases which Dohan and Heller and Alvri included in their later reviews. The latter authors, however, omitted Bronson's case, reported in the *Transactions of the American Dermatological Association* in 1901, and included in Dohan's report; in this instance the gangrene involved the right cheek, neck, ear, clavicle and thumb. Durand and Bobillo⁴ have since reported (1935), a case of symmetrical gangrene of the lower extremities and superficial gangrene of the left forearm. The inclusion of these two cases and the addition of the case reported herewith bring to 43 the number of recorded cases, to 12 the number of cases of gangrene of the upper extremities, and to 7 the number of cases recorded in the American literature. It might be added that an examination of the literature, since 1941, has revealed only one possible additional case. It is in a German publication which is not available to me, and the title is not sufficiently specific to permit a definite statement that the case is one of gangrene of the newborn infant.

In addition to the 7 cases recorded to date in the American literature, 4 others have been reported in the English, and 1 in the Australian literature. No reasonable explanation presents itself for the preponderance of reports in the foreign literature. As in all "rare" conditions, undoubtedly many cases have occurred which have not been reported, but there also seems no doubt that gangrene of the newborn infant is actually very rare. The subject is not mentioned in textbooks of obstetrics, and 11 leading obstetricians in the United States who were questioned concerning it replied that they had never observed it or even heard of it, though all of them had had personal experience with compound presentations.

The only case in any way similar to my own and the other reported cases observed by any member of this group was described by Dr. J. W. Harris.⁵ A child delivered after a prolonged dry labor presented just above the knee a spiral depression completely encircling the thigh, into which the umbilical cord fitted with ease. Below the depression the leg was enormously edematous, cold, and almost black. Gangrene seemed inevitable, but recovery ensued under conservative therapy. The condition was explained as due to interference with the circulation by the umbilical cord which encircled the thigh.

In the 43 cases reported to date, the outcome is in doubt in 5 instances, and 16 children are known to have died of the condition. Deferred death occurred in my own case, but it is highly doubtful that the gangrene had any part in the fatality.

The most baffling feature of gangrene of the newborn infant is the etiologic factor. In certain of the reported cases the suggested causes are unconvincing. In Cotes-Predy's⁶ case, for instance, maternal trauma is advanced as the cause of fatal fetal gangrene, the mother having fallen on the right side twice before delivery. The evidence advanced for the diabetic etiology suggested in Lawrence and McCance's⁷ case is of dubious worth, and Raynaud's disease, suggested as a cause in 4 reported cases, is unlikely in newborn infants, for obvious reasons. Infection was a reasonable possibility in some though not in all of the cases in which it was suggested.

The most logical cause suggested in the reported cases was trauma at delivery. As Heller and Alvri point out, the incidence of hard, difficult labor, abnormal delivery and neonatal asphyxia in the 40 cases they collected is far above the proportion to be expected in so small a series. In the 39 cases in which details were available, labor

was difficult or birth instrumental or otherwise abnormal in 11 instances, the cord was about the child's neck in two instances, and the baby was asphyxiated, or otherwise abnormal in 8 instances.

It is interesting that the majority of obstetricians who were questioned on the subject, as previously mentioned, advanced trauma at delivery as the most reasonable explanation. Bayard Carter,⁸ for instance, reasoned that if pressure necrosis of the scalp can occur, it seems logical that pressure on the prolapsed extremity in a compound presentation can produce the same result. A. C. Beck⁹ stated that he always discusses pressure necrosis as a theoretical possibility in prolonged labors with prolapse of the hand when he is lecturing to students. In his opinion gangrene would occur more often except for two circumstances, that many cases are promptly recognized and treated either by replacement of the hand or by version, and that there is a high percentage of stillbirths in such cases.

In my own case, there seems little doubt that the gangrene can be attributed to prolonged pressure on the prolapsed hand caught between the head and the bony pelvis. It can reasonably be assumed (though no pelvic examination was made at the time), that the hand prolapsed at the time the membranes ruptured and that the pressure was continuous until delivery 50 hours later. A somewhat similar case was reported by Fischer¹⁰ in 1929: The midwife who attended an 18-year-old primipara stated that after 14½ hours of hard labor, the child was born with the palm of the right hand over the right eye, and with the umbilical cord around the neck. Gangrene was apparent a week after birth, but the child was not seen until the eleventh day; his condition then did not permit amputation and death occurred on the fourteenth day. Postmortem examination showed thrombus-formation in the great vessels of the right arm, pulmonary arteries and aorta. In my own case, pathologic examination of the amputated extremity failed to show thrombus-formation.

In my own case, there was ample amniotic fluid, and amniotic adhesions could not have caused the gangrene. It is unlikely that it was due to focal deficiencies, as studied by Streeter,¹¹ for in such cases, as he pointed out, "the defect usually is present in some degree in all four extremities, and at least in two or more."

Heller and Alvari have outlined a plausible and ingenious mechanism to explain the gangrene in their personal case. Delivery was by midforceps, resorted to after 29 hours of hard labor because of maternal exhaustion. The child was in poor condition at birth and presented cyanosis and asphyxia. The following day the right arm was found to be paralyzed and the right hand was cold, limp and blue. Two days later a gangrenous process involved practically the whole right upper extremity below the elbow, and pulsation could not be detected in either the axillary or radial artery. Amputation was considered and decided against, and conservative treatment was instituted, with ultimate preservation of the extremity and with only limited loss of function.

These authors do not believe that if true thrombus-formation had been present, canalization could have been established in so short a time. They also point out that freeing of a thrombus would have resulted in a more dramatic episode distal to the axillary artery than that which occurred, and that rapid establishment of collateral circulation need not be assumed, because the axillary artery resumed pulsation six days after birth.

Their hypothesis is that "there existed a temporary agglutination of the intimal surfaces of the large vessel . . . similar to that which occurs when a piece of rubber tubing of equivalent caliber is pressed on firmly for a protracted period. Perhaps the surfaces were sealed with fibrin, which essentially shut off all distal supply of blood but was not necessarily accompanied by thrombus-formation. When the pressure was no longer a factor, the proximal pulsating blood stream

acted as a hydrostatic wedge, and the adhered surfaces gradually were forced apart and circulation again established soon enough to preserve function but not before a modicum of damage had been done."

This hypothesis seems more generally applicable than any other which has been suggested. It is particularly applicable to the cases of gangrene of the extremity in which recovery occurred under conservative treatment, and it is also applicable to the cases in which amputation was necessary or in which no surgery was practiced and death occurred. In such cases, as in my own, the pressure may have lasted too long to permit separation of the adhered surfaces after it was relieved.

Heller and Alvari, on the basis of this hypothesis, suggest that in the absence of gross infection, a mutilating procedure should be postponed until it is certain that it cannot be avoided. The advice, of course, is sound, for amputation of an extremity is a repugnant operation at any age, and particularly repugnant in a newborn baby. On the other hand, it sometimes cannot be avoided. In Heller and Alvari's case, pulsation in the axillary artery was felt on the sixth day and pulsation of the radial pulse on the twelfth day, but in my own case these pulsations, originally present, disappeared under conservative therapy and the gangrenous process continued to spread. The warning should also be uttered that in one's natural desire to be conservative, radical surgery should not be delayed too long, as it apparently was in some instances in the reported series in which death occurred without operation.

Diagnosis is usually clear-cut. In my own case, as in Heller and Alvari's case and in one of the cases reported by Lévy,¹² limitation of motion, which in my own case and in Heller and Alvari's case amounted to actual paralysis, was antecedent to the gangrenous process, and in such cases, as Lévy notes, Parrot's pseudoparalysis must be differentiated.

The practical importance of this case report is, as E. D. Plass¹³ points out, the recognition of "a new danger from premature rupture of the membranes." It is the practice of many obstetricians in such instances to avoid pelvic examination until after pains have begun and labor has progressed, and that practice was followed in this instance. It may be that under such circumstances immediate pelvic examination might be the wiser plan.

Summary

A case is reported of gangrene of the upper left extremity in a newborn infant, born 50 hours after rupture of the membranes and two hours after the onset of labor; at delivery the affected extremity was found prolapsed between the cranium and the bony pelvis. Conservative therapy was ineffective and amputation was necessary on the eleventh day of life.

To date, 42 similar cases have been reported in the literature, of which 11 were instances of gangrene of the upper extremity.

The etiology is briefly discussed, and trauma is shown to be the most reasonable and most generally applicable cause of the condition.

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ADENOACANTHOMA OF THE OVARY

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THE term adenoacanthoma is applied to tumors composed of glandular and squamous elements;¹ these neoplasms are sometimes known as adenoacanceroids. Descriptions of such lesions encountered in the esophagus, stomach, gall bladder, pancreas, sigmoid, thyroid, and lung have been reported sporadically in the literature. The fact that occasionally, carcinomas of the corpus uteri are composed of both glandular and squamous cells is well known. Among 100 cases of carcinoma of the body of the uterus, Healy and Cutler² found 3 adenoacanthomas. Lindsay,³ in 1927, reported 3 instances of adenoacanthoma in a series of 70 cases of corpus carcinoma. The occurrence of metastatic adenoacanthoma of the ovary from a primary adenoacanthoma in the body of the uterus is mentioned by Meigs.⁴ The authors have been unable to find a single instance of primary adenoacanthoma of the ovary in the literature at their disposal. Inasmuch as two patients, who presented such a neoplasm, were encountered recently on the gynecology service of University Hospitals, it is felt that the reporting of such an unusual lesion would be in order.

Case Reports

CASE 1.—(History No. 225-530; Pathology No. 74739.) This was a 69-year-old white housewife, who was admitted to the gynecology service of University Hospitals with a complaint of vaginal bleeding for one month. The bleeding had been intermittent, and there had been no clots; no pain; no weight loss. The patient gave a history of having had scarlet and typhoid fevers. There had been two normal pregnancies; no abortions. Review of systems was not revealing. The menses began at the age of 13 years, and occurred regularly every 28 days, lasting for 7 days. The last menstrual period was 26 years previously. Physical examination revealed a healthy appearing elderly white woman, in no particular distress. The findings on general physical examination were entirely within normal limits. Pelvic examination, however, disclosed a relaxed vaginal outlet; cervix anterior and atrophic; fundus uteri forward and apparently normal. Both adnexal regions were occupied by firm, nodular tumor masses. On laboratory examination, the urinary findings and blood count were within normal limits. Radiogram of chest showed no evidence of parenchymal infiltration in the lung fields.

On November 23, 1942, pelvic laparotomy was carried out under gas-oxygen-ether anesthesia. The left ovary was nodular and cystic, and measured 14 cm. in greatest diameter. The ovarian mass was adherent to the broad ligament anteriorly, and the left Fallopian tube was drawn out over its superior surface. The corpus uteri was entirely normal in size, color, and consistency. The right ovary, however, was the size of a man's fist, and was white and glistening in appearance; it was nowhere adherent. Bilateral oophorectomy and left salpingectomy were carried out; however, because of the patient's unsatisfactory condition under anesthesia, hysterectomy was not undertaken. Following operation, the patient made a satisfactory convalescence, and was discharged from the hospital on the twenty-first postoperative day. Despite the exhortation of the staff, the patient refused to undergo diagnostic curettage before going home. This procedure was urged so that the absence of

corpus cancer could be definitely established, despite the fact that there was no clinical evidence of such a lesion.

Pathologic Examination.—The (left) ovary weighs 735 Gm., and measures 14 by 11 by 6.5 centimeters. The external surface is relatively smooth. Occasional daughter cysts varying from 2.5 by 2 to 6 by 4 cm. contain light-brown, glairy material. The ovary is essentially a sac, and varies from 0.5 to 1 mm. in thickness. Sections taken through the cystic portions show the cystic spaces to vary considerably in size. They are all lined with columnar epithelium that in most instances is a single layer in thickness. These cells are fairly uniform in type and many are ciliated. Sections from other portions of the ovary show tumor which is pleomorphic and of epithelial type. Throughout there are papillae with slender connective tissue cores, that are covered with columnar epithelium. There are numerous glands that vary considerably in size. The glands are lined with columnar epithelial cells. Some of these cells have atypical irregularly shaped hyperchromatic nuclei and others have mitotic figures, some of which are abnormal. In addition throughout, there are groups of cells that are definitely of squamous type. In some regions there is considerable keratohyaline material. The tumor is definitely invasive, there being identifiable glands lined by tumor cells situated in the ovarian stroma.

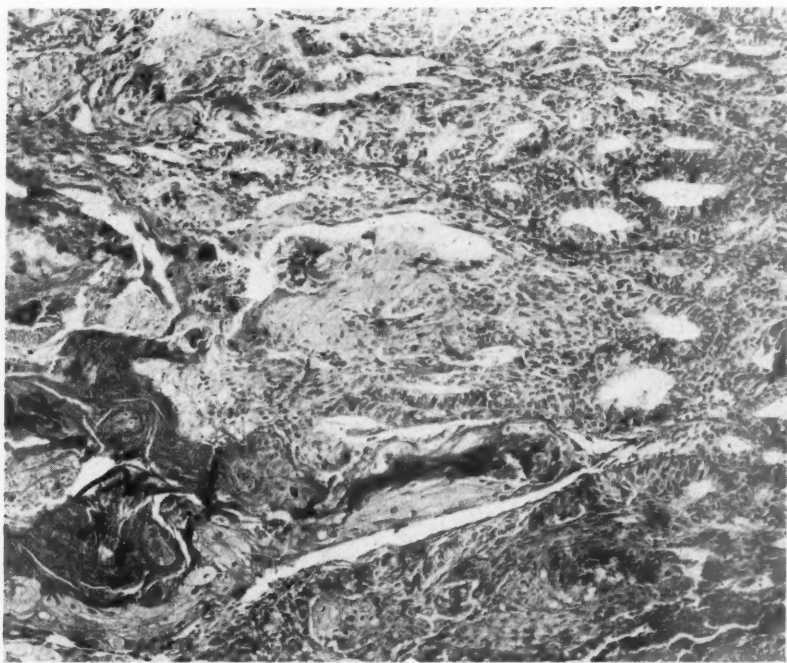


Fig. 1.—Case 1. Adenoacanthoma of the ovary. Photomicrograph ($\times 120$) showing large plaques of squamous epithelium, containing abundant keratohyaline material. Sections from Case 2 are strikingly similar to those from Case 1, except for slightly less squamatization.

The tube measures 12 by 0.6 centimeters. It is smooth reddish gray, and the fimbriated end is occluded and adherent to the ovary. The lumen is patent, empty, and is not dilated. The wall is not unusually thickened. Sections of the uterine tube show the lumen to be patent. The plicae are unusually large, and some are club-shaped. They are covered with simple columnar epithelium. There is no significant cellular infiltration in the sections examined.

The (right ovarian) tumor mass weighs 180 grams and measures 9 by 6 by 5 centimeters. The external surface is unusually smooth and light-pinkish gray. The cut surface neither bulges nor retracts, and is pearly gray. There is no obvious degenerative change. Sections show the tumor mass to be richly cellular and definitely edematous. The cells

vary in size and shape; some are elongated and spindle in outline. These have acidophilic cytoplasm. Others are somewhat stellate in type, and some are oval. They have relatively large nuclei, many of which are irregularly shaped and deeply chromatic. There are no bizarre nuclear forms, or abnormal mitotic figures. The tissue separating these cells is loosely arranged, of connective tissue type, and is distinctly edematous.

Diagnosis:

1. Papilliferous serous cystadenocarcinoma of ovary, showing marked squamous metaplasia.
2. Fibroma of other ovary.
3. Healed salpingitis.

Since operation (November 23, 1942), the patient has been entirely asymptomatic: there has been no abdominal pain; no vaginal discharge or bleeding; and, no loss of weight. Vaginal examination at this time (August 28, 1944) reveals an atrophic uterus, and entirely negative adnexa. Thorough uterine curettage was done on August 28, 1944, but hardly any tissue was obtained. The pathologic report on the surgical specimen was "material insufficient for diagnosis."

CASE 2.—(History No. 235-207; Pathology No. 83273.) This was a 61-year-old colored cook, who was admitted to the gynecology service of University Hospitals on April 24, 1944. The patient's chief complaint was lower abdominal swelling for three months. The patient stated that during the course of her illness, there had been a gradually enlarging tumor in the lower left abdomen. Aside from the tumor, the only other symptom had been recurrent bouts of lower abdominal pain. The patient gave a history of a pelvic laparotomy, in which the right ovary is alleged to have been removed, 30 years previously in another state. Past history included but one pregnancy, which was said to have terminated in early abortion. In 1934, duodenal ulcer was diagnosed at this hospital. Menopause occurred in 1927, since which time there has been no vaginal bleeding.

At the time of admission to the hospital, the patient appeared normally developed and well nourished. General physical examination disclosed the heart to be somewhat enlarged to the left and a systolic murmur could be heard over the base of the heart. Blood pressure was 160/110 mm. mercury. On abdominal examination, a remote lower midline surgical scar was seen. An obvious mass occupied the entire lower left abdominal quadrant. The tumor was tensely fluctuant in consistency, and not especially tender. Liver, spleen and kidneys were not palpated, and there was no evidence of free abdominal fluid. On pelvic examination, the outlet was marital, but well supported. The cervix was clean and anterior. The corpus uteri was taken to be about normal in size, and could be palpated separately from the tumor mass in the left adnexal region. The mass was fluctuant but not tender. Nothing abnormal was made out in the right adnexal region. Results of urinalysis were negative. Erythrocytes numbered 4,000,000 and the value for hemoglobin was 67 per cent (Sahli). Results of the serologic test for syphilis were negative.

On April 25, 1944, pelvic laparotomy was carried out with the patient under the influence of gas-oxygen-ether anesthesia. Lysis of adhesions, subtotal hysterectomy and left oophorectomy were performed. The mass described above proved to be a left ovarian cyst; it was adherent to loops of small bowel in several places, and adherent to the sigmoid and posterior surface of the uterus. The right adnexal structures were found to be missing from a previous operation. The patient withstood the operative procedure fairly well, and was returned to bed in satisfactory condition. The postoperative course was interrupted by mechanical bowel obstruction, which required laparotomy and the lysis of

adhesions on the fifteenth postoperative day. Subsequently, the patient developed pleurisy with encapsulated effusion, which gradually resorbed. However, the patient was discharged from the hospital in satisfactory condition on the fortieth hospital day.

Pathologic Examination.—The ovarian tumor measured 13.5 cm., and grossly showed a striking resemblance to the carcinoma removed in Case 1. Microscopically, sections of the ovary show the tumor to be of epithelial glandular type. The glands are lined with high columnar epithelium and vary greatly in size. Irregularly shaped hyperchromatic nuclei render many of the epithelial cells atypical. Some of the mitoses are abnormal. There is a focal distribution of identifiable acidophilic keratohyaline material. Extensive necrosis and infiltration with neutrophilic polymorphonuclear leucocytes may be seen in some fields. Grossly, the uterus is atrophic; it weighs 30 grams, and measures 5.0 by 4.0 by 1.5 centimeters. Scattered through the myometrium are three firm encapsulated tumors, from 5 to 12 mm. in diameter. On section, these tumors have a bulging, white, whorled cut surface. The endometrium is intact, and is thin pinkish-white in color. The serosa is shiny and transparent.

Diagnosis:

1. Partially differentiated cystadenocarcinoma of ovary with focal squamous metaplasia, acute inflammation and necrosis.
2. Fibromyomas and atrophy of uterus.

Discussion

The histogenesis of adenosquamous carcinoma is a moot question. A voluminous literature has been written on the subject of adenoacanthoma of the body of the uterus. It is the conclusion of Novak⁵ that the "epidermization" seen in fundal adenoacanthoma is the result of metaplasia of the cylindrical to the squamous type of epithelium. A study of cervical biopsy material reveals the very great frequency of metaplasia of the normal columnar to the squamous type of epithelium, in inflammatory lesions of the cervix uteri. Moreover, it is recognized that the germinal epithelium covering ovaries which are involved in chronic perioophoritis occasionally undergoes squamous metaplasia.⁶ Then there is the condition known as cystic fibrosis of the pancreas in which, due to the impaired absorption of fat-soluble vitamin A, there is a pronounced squamous metaplasia of the bronchial mucosa.⁷ It would appear, therefore, that squamous metaplasia is really of rather frequent occurrence in a wide variety of pathologic processes, running the gamut from chronic inflammatory lesions, and a vitamin deficiency state, to frank neoplasms. It seems entirely tenable, therefore, to assume that the squamous elements in the ovarian adenoacanthomas here presented are, in fact, the result of the ubiquitous process of metaplasia.

Another plausible hypothesis for the presence of squamous epithelium in ovarian carcinoma is the supposition that such may result from Walthard's islands. According to Ewing,⁸ the latter are thought to result from the "invaginations of celomic epithelium." The manifold possibilities of celomic epithelium on differentiation are well known. It well may be that the origin of the squamous elements in ovarian acanthoma is identical with the generally accepted theory of histogenesis of Brenner tumor, viz., Walthard's cell rests.

Whether the squamous elements in the ovarian carcinomas described herein arise from squamous metaplasia or from Walthard's islands cannot be decided from our present-day knowledge of the histogenetic phenomena of the ovary. The authors, however, incline to the view that the squamatization seen in the tumors described is the result of metaplasia.

Summary

Two instances of a rare, primary ovarian neoplasm, adenoacanthoma, have been reported. The various histogenetic possibilities regarding the

origin of squamous elements in columnar epithelial carcinoma of the ovary have been discussed.

It is suggested that the term adenoacanthoma be used in naming these peculiar ovarian carcinomas, in keeping with the use of this term in the designation of adenosquamous tumors elsewhere in the body.

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OMPHALOCELE (AMNIOCELE)

Its Anatomy and Etiology in Relation to Hernias of Umbilicus and the Umbilical Cord

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THE incidence of omphalocele has been reported generally to be about 1:5,000 deliveries. This holds true for the case reported below, it being the second instance in 10,620 deliveries in this hospital since 1924. The first case was published by Jarcho,¹ who reviewed the literature on 400 cases to 1937. Since that time, more than 50 cases have been published, Ladd and Gross² alone reporting 22 cases from the Children's Hospital in Boston.

An unusual appearance for the obstetrician who encounters it for the first time, the cases look very much alike when one reviews the photographs published with the reports. In the typical omphalocele, the abdomen cranial to the supposed site of the navel is involved, never the lower abdomen. In many of the cases, there are no other malformations of the abdominal organs; smaller or larger parts of the small intestine and of the fetal liver are visible through, and during increased intra-abdominal pressure protrude into, an amnion-covered sac, the amount depending on the size of the defect in the abdominal wall which varies from 5 to 10 cm. in diameter.

The name "omphalocele" used for this congenital malformation by most of the authors in the latest publications (although "amniotic hernia" or "amniocele" would be more appropriate) should be applied to this anatomical and formational entity involving the supra-umbilical part of the abdomen, to differentiate it from a hernia into the umbilical cord in which a single loop of intestine, liver or omentum protrudes through a small ring into the cord, and from the true umbilical hernia covered by skin. As discussed later, these different structural defects do not seem to be simple gradations of the same condition, but originate at different stages of the developmental periods of embryonic life.

There is now a consensus of opinions that the only feasible way to save the life of the infants born with omphalocele is a surgical repair as soon as possible. The results depend on the skill of the surgeon, on

the time elapsed between birth and operation (at the latest 36 hours, because the thin amniotic membrane must not be allowed to dry out), and on the size of the sac. Ladd and Gross² point out that in their large series, they had 75 per cent survivals in patients with a sac less than 8 cm. in diameter, and only 15 per cent when the sac was larger than 8 cm. in diameter. The babies tolerate the open ether anesthesia very well and, where the approximation of the edges of the recti muscles is possible and will not be carried out too far cranial so as to interfere with the baby's breathing, which becomes impaired anyhow by the increased intra-abdominal pressure, the patients will most probably survive.

Case Report

A male, full-term, 8-pound, 4-ounce baby, was delivered by elective low-flap cesarean section on January 6, 1944. (Case history 81565.) The indication for the cesarean section was a double footling presentation in a 38-year-old, white, para 0, gravida ii. The pregnancy was uneventful and closely watched because the patient had gone through a period of essential hypertension up to 170/100, during several months subsequent to a pyelotomy for removal of a stone in October, 1941. She followed the contraceptive advice until normal blood pressure was established for 6 months. During the last trimester of the pregnancy, the fetal heart was always arrhythmic, of an extrasystolic type.

The delivered baby showed a huge, rounded defect in the abdominal wall occupying almost the entire upper and midpart of the abdomen, and covered by a thin translucent amniotic membrane in an area 10 by 8 centimeters. The umbilical vessels ran between the amniotic membrane and the peritoneum, and converged in the left lower quadrant to form a normal umbilical cord. Through the moist transparent membrane one could differentiate the left lobe of the liver in the upper part, and coils of small intestine in the lower part, of the defect. When the baby cried, the liver and the intestine became eviscerated into the sac, the bulging attaining the size of a large orange. During the crying, there was, moreover, a bulging of the skin-covered part of the epigastrium showing the complete diastasis of the recti muscles. The abdominal skin seemed abundant and creased around the sac and separated from the amnion by the physiologic red demarcation line. The anus was open and contained meconium. The baby seemed otherwise very well developed, and showed no other malformations except for an arrhythmic heart action. The umbilical cord was tied and cut, and a sterile dressing applied. Twenty-four hours later, the baby was operated on by Dr. A. Salvin under open ether anesthesia. The brim of the skin was circumsized and the fascia of the recti muscles freed. The recti abdominis muscles showed a complete diastasis in their upper thirds and converged toward the midline to unite right below the mid-abdomen. The peritoneum was entered, its margin circumsized and removed together with the membrane covering the evisceration. The closure of the gap, although difficult, was then accomplished in vertical direction (the liver was not adherent). A second row of enfolding fascial sutures was placed, and the skin approximated with silk sutures.

During the operation and with the dressing afterward, pains were taken not to interfere with the baby's breathing. Thus, the upper edges of the recti were not approximated and the dressing was loosely applied over the thorax.

The baby was put into an incubator with oxygen supply, 20 c.c. of maternal blood injected intramuscularly, several hypodermoclyses of 5 per cent glucose in saline 100 c.c. each time given during 48 hours. Mouth feeding was resumed on the third postoperative day, $\frac{1}{2}$ ounce of formula every 2 hours day and night, and increased by $\frac{1}{2}$ ounce every second day. Highest rectal temperature was 101.2° F. on the second postoperative day, and became normal from the fourth day on. Weight dropped to 7 pounds, 6 ounces on the fifth postoperative day, and from the seventh day on, the baby gained constantly and weighed 7 pounds, 12 $\frac{1}{2}$ ounces on the day of discharge. The extrasystoles disappeared

after a few days and an EKG taken 6 days post partum showed: Sinus tachycardia, rate varying from 136 to 160 in the various leads. P-R interval 0.10 second. Right axis deviation. QRS of low amplitude in the limb leads. Q-3 present. RS-T segment depressed in leads IV and V. T-I iso-electric, T-R low, T-4 and T-5 inverted: the abnormalities noted probably due to a poor functional state of the cardiac muscle. Unfortunately the EKG has not been repeated.

Mother and child were discharged in good condition on the thirteenth day after delivery. Seen last, 5 weeks after the operation, the baby weighed 9 pounds, 12 ounces. The abdominal wound healed by primary union and the repair of the omphalocele was in good condition. There was only a shallow pit below the ensiform process during inspiration and crying. Heart action was regular.

Follow-up Note.—While this paper was being prepared, I was notified that the infant which had been growing and developing normally, suddenly died "apparently from an acute heart failure" on March 28, 1944. No autopsy was obtained.

Discussion

Lately, the conception on the formal genesis of omphalocele has changed from the assumption of the primitive intestinal loop failing to withdraw into the celomic cavity toward the end of the third month of embryonic life (Jarcho¹), to the explanation that the cause may arise from a disparity between the size of the abdominal viscera and the abdominal cavity, resulting from a retarded development of the abdominal parietes. (Bergglas,³ Gross and Blodgett,⁴ Ladd and Gross,² Specht and Shryock.⁵) Aside from reports on cases and discussions on the cause, there exist two large monographs on malformations of the ventral wall of the trunk, Kermauner's⁶ and Sternberg and Politzer's.⁷ Kermauner generalized the cause of all clefts of the ventral wall and related them to retardation of or fault in, development of the different metameres of myotomes which begin to spread ventrad from the primitive spine in the third week. He denied any correlation between the development of abdominal parietes and the withdrawal of the primitive intestine and also disapproved the idea, that increase or even excessive growth of the viscera could be a causative moment for the formation of a congenital hernia. By stating that "the amniotic covering of the hernial sac corresponds to the somatopleure, the lower membrana reuniens," he accepts Aschoff's⁸ and Neugebauer's⁹ opinions that the covering of the upper part of this kind of hernia does not represent the dilated base of the navel, but that it corresponds to the upper part of the anterior abdominal wall, arrested in its development. Still he generalizes the causes of the different structural defects in the ventral wall of the trunk on the base of His' theory of concrescence of the two halves of the body in the ventral midline. He contends, however, that at that time (1909), "there is only little knowledge about the details on morphology of the definite closure of the abdomen."

Since that time, two basically important papers on the formation and closure of the anterior abdominal wall in normal human embryos have been published (Pernkopf,¹⁰ Politzer and Sternberg¹¹). The last two authors examined the formation of the umbilical pedicle and that of the anterior abdominal wall on embryos from 2.3 mm. to 9.5 mm. length, while Pernkopf's paper deals with the formation of viscera and with closure of the umbilical ring in fetuses up to 50 mm. length. Politzer and Sternberg show that the ventral wall of the trunk is formed in a very complicated way in several portions: the pericardial, supra-umbilical, umbilical, subumbilical and genital parts and at different times. In their monograph,⁷ where they also report a case of omphalocele with severe other malformations, they discuss the formal genesis of malformation of the respective parts of the ventral wall of the trunk based on the knowledge derived from their first paper.

Due to the curling of the 1.5 mm. embryo, the anlagen of organs built from the mesodermal field as the heart and liver, rotate around a trans-

verse axis and parts which primarily lay craniad are shifted ventrad and then caudad. At the same time, the embryo is being enveloped by the amnion sac which ensheathes the body stalk and thus forms the extracelomic cavity. According to Politzer and Sternberg, there is one stage in this development (in embryos of 6 to 7.5 mm.) where the later cranial amniotic covering of the abdominal pedicle ("amniotische Deckplatte") forms the outer layer of and unites with, the transverse septum, a part of the mesodermal field from which a portion of the pericard is formed and into which the liver cells grow in. Later, in embryos of 9 mm. length, due to the prolific growth of liver cells on the dorsal part of the transverse septum and to proliferation of connective tissue from its ventral part, this amniotic covering has been shifted caudad to form the cranial covering of the umbilical pedicle. It thus gives way to the formation, from the transverse septum, of the supra-umbilical portion of the abdominal wall, which then consists of embryonic connective tissue covered by ectoderm.

This means that the later supra-umbilical part of the abdominal wall, the only part of the body surface save for the navel, has a transient covering of amnion and the two authors relate the origination of omphalocele to a disturbance in development of this amniotic covering. The close interrelation in the development of this amniotic covering, of the fetal liver and of the heart on, into and from the transverse septum, respectively, accounts for the presence of the liver in at least two-thirds of the cases and the frequent malformation or adhesions of the liver as well as for the defects of the heart, or even its presence in the gap.

The two authors do not try to explain how this disturbance in development may arise. In my opinion, the formational irregularity must lie in the relation of this amniotic covering to the underlying connective tissue of the transverse septum. Normally, the amniotic covering becomes closely adherent to the transverse septum in the earliest stage of their contact, although the two structures can be easily distinguished histologically even in the later stages. If, by mere chance, these two structures fail to coneresce, or if the connective tissue of the transverse septum fails to proliferate and thus to push the amniotic covering caudad toward the umbilical pedicle, an amnion-covered gap will be left open in this supra-umbilical part of the abdominal wall and result in the structural defect of an amniocoele.

At this stage of development (beginning of the third week), the myotomes have hardly started to spread ventrad. In the course of the sixth to eighth weeks, the abdominal muscles are differentiated from the myotomes and spread ventrad within the embryonic connective tissue which also serves to form the firm aponeurosis of the linea alba. In cases of the above-described aberration, however, the recti muscles are hindered to assume their normal relation, because there is no medium (connective tissue) in which they normally grow, and thus, they only surround the gap. Studies of Pernkopf¹⁰ show that the recti muscles do not take active part in the closure of the abdominal wall because long after retraction of the intestinal loops from the extracelomic cavity and after closure of the umbilical ring (fetuses of 50 mm. and more), the recti muscles still run V-shaped and are completely diastatic in their upper and midportions. The umbilical ring is formed by proliferation of the adventitial connective tissue of the umbilical vessels which process also aids the retraction of the extracelomic peritoneum. Moreover, according to Tandler,¹² the diastasis of the upper recti muscles is a physiologic feature in newborn and in young children. Based on these studies, we can discard Kermauner's hypothesis that all malformations of the anterior wall of the trunk are caused by an arrested or retarded development of the corresponding myotomes. The same applies to the assumption of others, that the formation of an omphalocele may be due to a disparity between the size of the abdominal viscera and the abdominal cavity resulting from a retarded development of the ab-

dominal parietes because, once the supra-umbilical part of the abdominal wall has been formed normally, no herniation covered by amnion can develop on this spot.

We can also relinquish the view that an omphalocele is due to the failure of the primitive intestinal loop to withdraw into the abdominal cavity, because omphalocele is a malformation of the supra-umbilical portion of the abdominal wall and not one of the umbilicus proper.

Real hernias into the umbilical cord are caused by either a failure of the abdominal contents to retract from the extracelomic cavity at the right time, or by a failure in the proliferation of the adventitial connective tissue of the umbilical vessels with resulting primary hernial sac and secondary herniation of the abdominal contents. Both aberrations occur as can be judged from cases of incarceration of intestine or liver in congenital umbilical hernia (failure of withdrawal at the right time and normal proliferation of connective tissue), or from cases of free hernias (failure of proliferation of connective tissue and of retraction of extracelomic peritoneum). The time at which these hernias develop is the eighth to tenth weeks (fetuses of 45 to 50 mm. length) and as the supra-umbilical part of the abdomen had been formed normally in the third week, these cases show normal anatomy of the upper abdominal aponeurosis and the recti muscles.

We must, of course, realize that the omphalocele always involves the umbilical region of the abdominal wall. In the same way as the lack of connective tissue hinders the approximation of the recti muscles, it causes also the cranial circumference of the umbilicus proper to remain open. The extracelomic cavity cannot be closed in its upper part because it lacks on this spot in connective tissue which in normal cases is derived from the ventral part of the transverse septum, the later supra-umbilical part of the abdominal wall. But immediately below the navel, the recti muscles are completely approximated which proves that the different portions of the abdominal wall are formed independently.

Summary

1. A case of omphalocele is reported, operated 24 hours after delivery, with recovery.

2. Etiology of amniocele is discussed and assumed that it may be due to either a failure of union of the mesodermal transverse septum with its amniotic covering, or to a failure in proliferation of embryonal connective tissue in the transverse septum, processes in the third week of embryonal development, which normally lead to formation of the supra-umbilical part of the abdominal wall.

3. Omphalocele (amniocele) is defined as an anatomical and formational entity, a malformation of the supra-umbilical part of the abdominal wall and is differentiated from hernias into the umbilical cord.

4. The time of origin of this structural defect is confined to the third week of embryonal development, contrary to formation of hernias into the umbilical cord which develop in the eighth to tenth weeks.

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A RECTAL MANEUVER FOR PLACENTAL DELIVERY

With Observations on Rectal Palpation in the Third Stage

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THE determination of the presence or absence of the placenta in the birth canal and its delivery therefrom if incarcerated, can be accomplished rectally.

It is often difficult to determine the location of the placenta during the third stage. The classic signs of placental separation usually disclose whether the placenta has separated or not, but they do not tell whether the placenta is being harbored by the uterus, or by the vagina. When

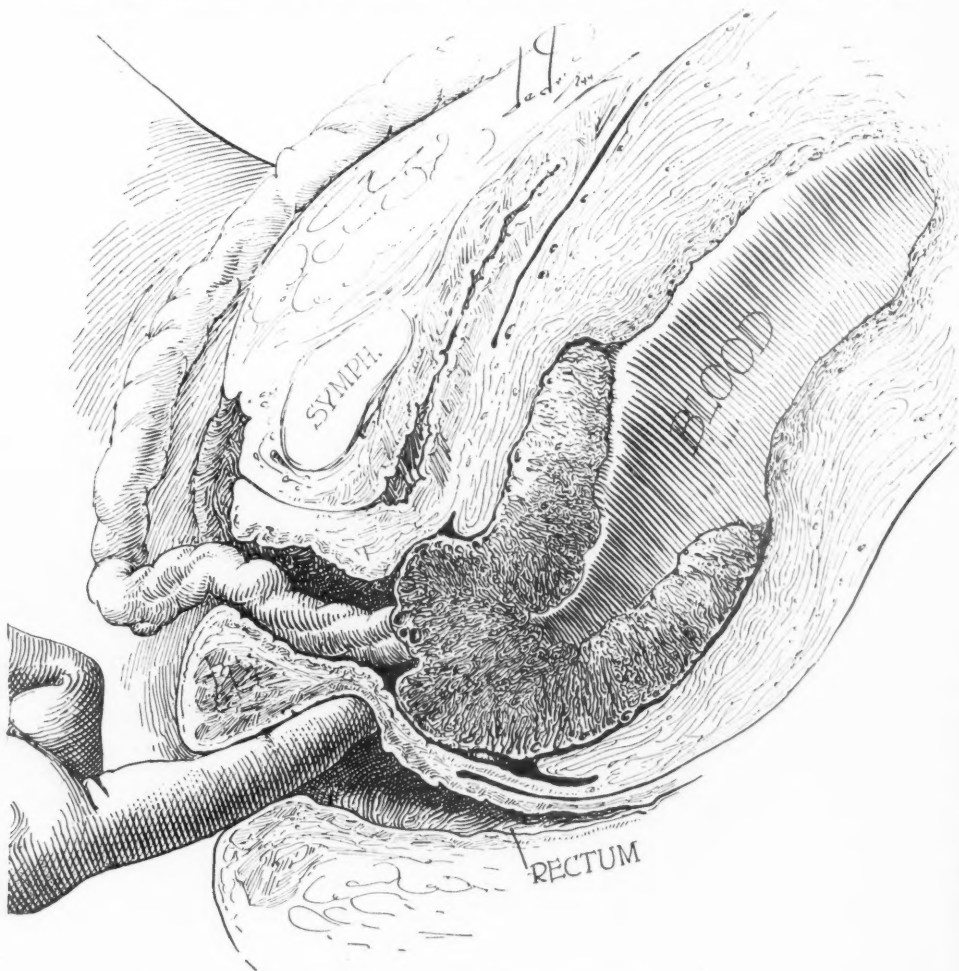


Fig. 1.—Diagnostic rectal palpation.

placental delivery is delayed, this is often a perplexing problem, and one that invites promiscuous vaginal examinations in the third stage. The vaginal examination reveals, of course, whether the placenta is intra- or extrauterine, but each vaginal examination is an invitation to puerperal infection, and any method which would reveal the same information



Fig. 2.—Rectal maneuver, step one: Hooking finger around placenta.



Fig. 3.—Rectal maneuver, step two: Milking out the placenta by a stripping action.

without the danger of infection should be the one of choice. Such a method is readily available by employing rectal examinations (Fig. 1). Many unnecessary vaginal examinations would be eliminated if, prior to attempting a manual removal of the placenta in a prolonged third stage, a rectal examination were done to more definitely establish the location of the placenta.

Rectal examinations in the third stage not only are useful for establishing the location of the placenta, but also for permitting placental delivery by the examining finger, in the following manner: the finger is hooked around the placenta (the anterior rectal and posterior vaginal wall intervening between finger and placenta) and the placenta is milked out by a stripping action. (Figs. 2 and 3.)

Rectal delivery of the placenta is particularly useful in cases of delayed placental delivery due to placental incarceration in a birth canal which has a small primiparous introitus, or one which has been narrowed by a recently sutured episiotomy. Moreover, in cases of placento-vaginal disproportion due to oversized placenta, the placenta often requires vaginal extraction; such placentas can usually be delivered by rectal stripping. Delivery of the placenta by rectal stripping is also indicated in cases of atony of the multiparous pelvic floor, especially following prolonged anesthesia. A retained, separated placenta is not an infrequent complication of the administration of ergotrate prior to placental delivery. When the greater part of the placenta is retained by a tight lower uterine segment, the rectal maneuver will not suffice; when, however, the greater part of the placenta is in the vagina, and only a small part is retained in the uterus, then rectal stripping will usually deliver the placenta.

Summary

1. A rectal maneuver for aseptic delivery of the placenta incarcerated in the lower birth canal is presented.

2. The maneuver consists of hooking the examining finger around the placenta and milking out the placenta by a stripping action of the anterior rectal wall.

3. This procedure is advocated only when complete uteroplacental separation has previously taken place, and when delay in placental delivery is due to one of the following: (a) tight introitus, (b) placento-vaginal disproportion, (c) atony of pelvic floor, or (d) spastic cervical segment due to previous administration of ergotrate, partially retaining the placenta.

4. This method of placental removal is not advocated for routine management of the third stage.

5. Diagnostic rectal palpation in the third stage is recommended in cases of delayed placental delivery, because it is as informative as a vaginal examination without the associated risk of bacterial contamination.

6. In cases of delayed placental delivery, a rectal examination should be done to confirm the location of the placenta before attempting a manual removal.

The author wishes to express his thanks to Dr. Clyde L. Randall for his encouragement and advice, and to Mr. Melford Diedrick for the illustrations.

THE DIFFERENTIAL DIAGNOSIS BETWEEN FETAL AND MATERNAL HEART RATE

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IT IS not infrequent when listening to the fetal heart rate for doubt to arise whether what one hears is really the fetal rate, or that transmitted from the mother's heart. This particularly is noted in cases where there is a rapid maternal rate—100 to 140—which is not at all uncommon during labor, notably in the protracted ones with exhaustion. Difficulty most often arises when the maternal apex beat or pulse rate and the fetal heart rate are exactly alike. The question then presents itself as to whether we are dealing with a live fetus, or one that is dead with a transmitted maternal heart rate over the uterus.

The author has used the following technique for a number of years with gratifying results. It is based on the phenomenon of the respiratory arrhythmia. As is well known, the normal beat accelerates during inspiration and slows during expiration. This is due to a decrease of vagus activity with acceleration of the heart beat during inspiration, and an increase of vagus activity with slowing of the heart during the expiratory phase.

While listening to the fetal heart, preferably with the head stethoscope, the maternal pulse is palpated. Let us assume both rates to be the same. The mother is asked to take a deep breath and then to exhale forcibly and completely. During this expiration, it will be noted that the maternal pulse definitely slows up during the subsequent two or three beats. This slowing, of course, does not affect the fetal heart which continues to beat at its regular rate and rhythm. On the other hand, should the heart sounds over the uterus slow simultaneously with the slowing of the maternal pulse, then we are dealing with transmitted maternal heart sounds. The deductions in both instances are obvious—a live baby in the first instance, and one with absent heart tones in the latter.

Conclusions

A small point in the differential diagnosis between maternal and fetal heart rates is described. The technique takes advantage of the respiratory arrhythmia (sinus arrhythmia) of the mother. It has proved helpful in a number of doubtful cases.

The data upon which this paper is based have been collected during civilian practice.

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American Obstetric Services

THE CHICAGO LYING-IN HOSPITAL

THE Chicago Lying-in Hospital and Dispensary was founded by Dr. Joseph B. DeLee in 1895. A four-room flat at 1336 Newberry Avenue was opened on Feb. 14, 1895, as the first dispensary. The first home delivery was on Feb. 27, 1895. In October, two medical students began to live at the dispensary. In 1896 a training school for nurses was started and the first intern began working at the dispensary.

A house at 515 Ashland Boulevard, with a capacity of nine beds, was opened on Sept. 2, 1899, as the first maternity hospital, and the first hospital delivery was on Sept. 14, 1899. Many of the leading obstetricians and pediatricians of Chicago helped staff the dispensary and hospital.

A three-story building was completed in 1904 on the corner of Maxwell and Newberry Streets, which became known as the Maxwell Street Dispensary of the Chicago Lying-in Hospital.

A new building, the Mothers' Aid Pavilion (isolation unit) with a capacity of thirty beds and bassinets, was opened on Nov. 6, 1914. It was used as the maternity hospital until the main building with a capacity of 140 beds and 120 bassinets was opened in 1917. Approximately 3,000 women were delivered each year after completion of the main building.

The hospital in 1927 became affiliated with the new medical school of The University of Chicago. A new hospital and Mothers' Aid Pavilion located on the Midway were opened on May 29, 1931. The hospital is adjacent to the Albert Merritt Billings Memorial Hospital and other hospitals belonging to The University of Chicago Medical School.

The main building of the Chicago Lying-in Hospital is six stories high, containing 143 beds and 119 bassinets. There are nine labor rooms, four delivery rooms, and an operating amphitheater on the fifth floor. The sixth floor contains quarters for the interns and residents. There is a separate nursery for premature babies.

The Mothers' Aid Pavilion (isolation) is an adjoining three-story building containing 24 beds and 18 bassinets, a delivery and an operating room. The departmental research laboratories, library, and private patient offices are also in this unit.

The adjoining clinic building, known as the Max Epstein Clinic building, contains ten examining rooms with adequate clinical laboratories, basal metabolism room, and fluoroscopic and dental equipment.

The Women's Board of the Hospital, on July 1, 1938, deeded the hospital and its assets to the University. The Boards, both of the

Beginning with the article on "The Lying-In Hospital of New York," published in the February issue, the JOURNAL is presenting brief descriptive articles dealing with the leading institutions devoted to the care of obstetric and gynecologic patients. These articles will review the history, equipment, staffing, service statistics, and similar features, affording to our readers certain general information of the activities of hospitals in this field of practice. We trust that they will prove of interest and value.

The Editor.

Lying-in Hospital and of the Mothers' Aid Pavilion, have continued to serve in an advisory capacity and have also continued their financial support of both institutions.

The supervision and support of the Maxwell Street Dispensary were stopped by the hospital on June 30, 1932. However, it was continued by Dr. DeLee as the "Chicago Maternity Center." A home delivery service using the hospital as a base was opened in November, 1932. This was discontinued in March, 1943, because it was felt that better care of the patient and better teaching of student, intern, and nurse could be carried out in the hospital than in the home.

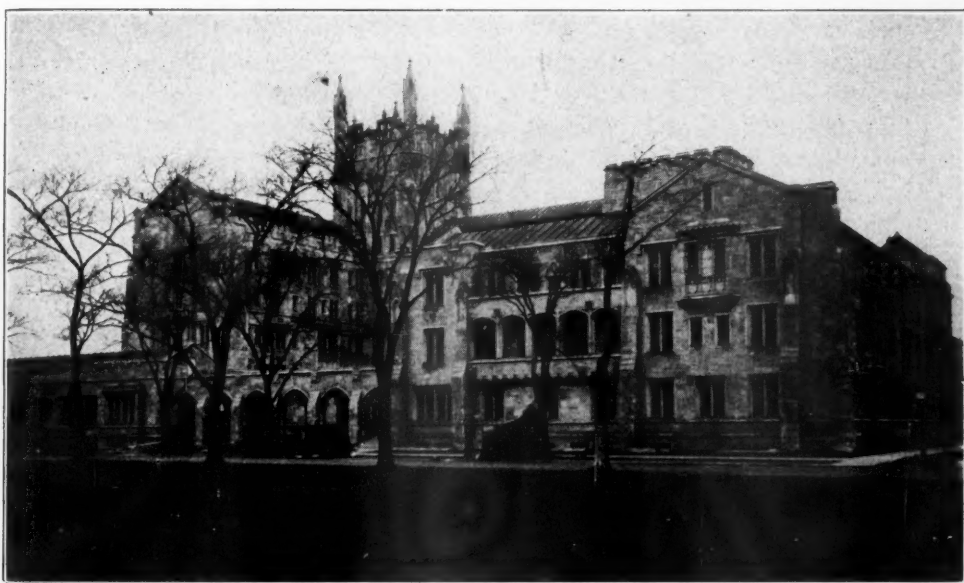


Fig. 1.—Chicago Lying-in Hospital, Mothers' Aid Pavilion, and Max Epstein Clinic Building.

The departmental staff before the war consisted of a professor, two associate and two assistant professors, four instructors, and four research associates, each a Ph.D., who supervised their respective laboratories—pathology, bacteriology, chemistry, and endocrinology. The house staff comprised six residents (four-year training) and sixteen interns (nine-month training), each of whom had had one or more years of hospital training prior to appointment. On April 1, 1943, first-year interns were accepted for a period of three months, the remainder of their time being spent in the other hospitals of The University of Chicago. The present staff consists of two professors (one is Chairman of the Department and Chief of Staff of the hospital), one associate and one assistant professor, an assistant professor of pathology, a research associate (Ph.D.) in chemistry, one instructor, and three instructors on leave of absence in the Armed Forces.

The courtesy staff consists of ten specialists in obstetrics and gynecology, known as the "Associate Staff," and approximately thirty additional doctors, some of whom are specialists, who comprise the eligible staff. These men have the privilege of bringing private patients to the hospital and participating in departmental conferences, but have no responsibility for teaching or care of staff patients.

The consultants for the hospital are the other heads of departments of the medical school.

The obstetricians retain control of the babies, but all care of the newborn baby is directed by members of the department of pediatrics of the University or qualified private pediatricians if the patient is a private patient.

The hospital has well-organized clinical laboratories and a department of pathology, which is under the direction of the professor of pathology in the medical school. The department of obstetrics and gynecology has its own special laboratories (chemistry, bacteriology, endocrine, and pathology) for research work and animal experimentation. The complete facilities of the basic science departments of the medical school are also available for special study and research. The hospital maintains its own diagnostic x-ray department under the supervision of the professor in the medical school. At Billings Hospital deep x-ray therapy is available, and the O. C. Miller radium clinic located in that hospital has 183 milligrams of radium in various applicators, suitable for the treatment of gynecologic patients.

The medical library of the hospital is a part of the University Libraries. It contains 3,800 volumes pertaining to obstetrics and gynecology and subscriptions to thirty special surgical journals and periodicals. A full-time librarian is in charge.

Almost half of the rotating intern's obstetrical service is on the birth room floor. The remaining time is given to the antepartum and postpartum care of women both in the clinic and the hospital, and to the care of the newborn under the direction of members of the department of pediatrics.

Graduate Training in Obstetrics and Gynecology

The department conducts well-organized prenatal and postnatal clinics, gynecologic clinics, and other special clinics for the care of these patients (toxemia, anemia, endocrine, sterility, lower genital tract infections, lipiodol visualization, tumor, maternal guidance, etc.).

First Year of Training.—Junior residents are limited to obstetrics, and at least one year of basic internship or its equivalent is required for the appointment. Two or more appointments are made quarterly on the recommendation of the chairman of the department. The first six months of the service are spent primarily in the clinic and hospital care of normal and abnormal pregnant and postpartum patients, some gynecologic patients, emergency anesthetics (the hospital has six full-time anesthetists) and newborn pediatrics. There is no home delivery service. The last three months are spent in the birth rooms where each resident is trained in the conduct of the third stage of labor, in the use of forceps, and the technique of episiotomy. He also assists the staff with private and abnormal cases. Full maintenance plus an annual stipend is provided. A health examination in our clinics is required before final acceptance.

Further appointments made each January and July to senior and chief residencies are based on the applicant's knowledge and clinical ability as shown during his junior residency. Full maintenance is provided during the residency plus an annual stipend which increases

from year to year. Each man is urged to participate in some research work. Following the chief residency an appointment may be made as instructor, usually on January 1 or July 1. The term of this appointment is for one year with full maintenance plus a salary.

The full-time departmental staff closely supervises all of the activities of the resident staff. The senior staff, consisting of three professors, rotates on the obstetric and gynecologic service, having a junior staff man as an assistant.

Second Year of Training.—During this year the senior resident will be first assistant to one of the senior staff in the care of his private and staff patients. All of his work will be in the Lying-in Hospital, the Mothers' Aid Pavilion, and the near-by Billings Hospital. He is responsible for the care of the patients under him as well as the supervision of the work of the intern and students on his service. Staff rounds are made daily.

Third Year of Training.—In the third six months the resident works full time in the various special laboratories of the department. He is taught the fundamentals in each of the laboratories. During the last half of the year the resident is in charge of the waiting and post-partum obstetric patients. He makes daily rounds with the obstetrician in charge and with the interns and the medical students. He assists in the delivery rooms.

Fourth Year of Training.—During the first six months the resident is in charge of the gynecologic service and arranges the daily operating schedule. He operates under the supervision of either the senior or junior staff gynecologist and at the end of this period is competent to perform major gynecologic surgery. He makes daily rounds with the gynecologist in charge of the service and with the senior residents, interns, and students.

During the last six months he is in charge of the obstetric service. Most of his time is spent on the delivery floor but he is held responsible for the care of all the obstetric patients in the hospital. He, with the assistance of two of the senior residents, must be present at all deliveries. At the end of his training he is a competent obstetrician and gynecologist and is qualified for certification by the American Board of Obstetrics and Gynecology.

Organized Study.—The department of obstetrics and gynecology holds weekly clinical conferences, conducted by the chairman of the department, for a review of the clinical work. Selected cases are reviewed, autopsy material is presented, and departmental problems are considered. The residents have an active part in preparing the programs for these conferences, presenting cases, and participating in the discussions. Facilities of the library are fully utilized in the preparation of these presentations.

Teaching Activities.—Each member of the resident staff has an active part in assisting the members of the faculty and the head of the department in supervising the clinical clerkships, in presenting cases when teaching rounds are made, and in assembling the material for the various teaching clinics. The senior and chief residents assist in teaching nurses and medical students.

Higher Medical Degrees.—No examination or thesis is required for the individual undertaking the usual course of graduate training in obstetrics and gynecology. If he is a candidate for a higher degree, either a Master's or Doctor of Philosophy, he must then comply with the prescribed requirements as to fundamental training and investigative work and must meet the requirements of the American Board of Obstetrics and Gynecology.

Pertinent data as to the number of deliveries, incidence of operative deliveries, and various major obstetric complications, as well as the maternal and fetal mortality are given in Table I, A. Our maternal and fetal mortality compare very favorably with other maternity hospitals. The hospital staff has always believed in prophylactic or out-

TABLE I
A. OBSTETRICS

| (NUMBERS OR PERCENTAGE) | | | | |
|---|------------|-----------------|-----------|-------------------|
| | 1931-1941 | 1941-1942 | 1942-1943 | 1943-1944 |
| Deliveries, 400 + Gm. | 27,321 | 3,236 | 3,813 | 3,581 |
| Abortions, less than 400 Gm. | 900+ | 57 | 69 | 173 |
| Maternal mortality, total | (50) 0.177 | (4) 0.124 | (4) 0.105 | (2) 0.056 |
| Morbidity, per cent | | 8.0 | 8.8 | 8.4 |
| Operative deliveries, per cent | 33.0 | 41.5 | 55.0 | 45.0 ^c |
| Cesarean sections, 400 + Gm. | 1,457 | 147 | 166 a | 151 a |
| Maternal Mortality | 10 | 1 | 0 | 0 |
| Breech deliveries, per cent | 3.8 | 4.3 | 5.2 | 2.7 b |
| Postpartum hemorrhage, per cent | | | 87 | 104 |
| Twenty-four-hour postpartum tubal ligation | | | 42 | 38 |
| Obstetric operations—not delivery | 1,029+ | 268 | 283 | 277 |
| FETAL RESULTS—PER CENT | | | | |
| Premature deliveries | 6.2 | 7.0 | 7.5 | 6.2 |
| Stillbirths | 2.26 | 1.83 | 1.96 | 1.62 |
| Term—2500 + Gm. | 1.06 | 0.77 | 0.79 | 0.78 |
| Premature—1,000–2,499 Gm. | 0.90 | 0.77 | 0.87 | 0.56 |
| Previa—400–999 Gm. | 0.29 | 0.29 | 0.32 | 0.28 |
| Neonatal deaths | 2.03 | 1.68 | 1.70 | 1.65 |
| Term | 0.70 | 0.31 | 0.55 | 0.56 |
| Premature | 1.06 | 0.83 | 0.95 | 0.84 |
| Previa | 0.26 | 0.52 | 0.20 | 0.25 |
| INCIDENCE | | | | |
| 1931-1944 | MORTALITY | | | |
| | INCIDENCE | MATERNAL NUMBER | PER CENT | FETAL PER CENT |
| Nonconvulsive toxemia and/or hemorrhage, nephritis infection, heart disease | 8.1 | 2 | 0.06 | 11.0 |
| Eclampsia | 0.22 | 9 | 0.29 | |
| Placenta previa | 0.63 | 4 | 5.8 | 26.0 |
| Abruptio placentae | 0.59 | 2 | 0.77 | 28.0 |
| Postpartum hemorrhage | 2.9 | 3 | 1.33 | 62.0 |
| Cesarean section | 4.74 | 4 | 0.36 | |
| Abortion—up to 399 Gm. or 22 weeks | 3.00 | 11 | 0.61 | *8.7 |
| | | 2 | 0.17 | |
| Uncorrected figures for all pregnant women admitted. 37,951 deliveries of 400 + Gm. 1,199 abortions—less than 400 Gm. or 22 weeks. a: 1,500 + Gm. b: 2,500 + Gm. | | | | |
| B. GYNECOLOGY | | | | |
| Operations | 6,216 | 640 | 555 | 518 |
| Mortality—includes terminal carcinoma | 65 | 6 | 3 | 5 |

let forceps (for the benefit of the patient and baby as well as for teaching), which explains the high incidence of operative deliveries.

The major portion of the operative gynecology is performed at the Lying-in Hospital in separate operating rooms. A small number of patients are cared for in Billings Hospital. Pertinent data are given in Table I, B.

The general and private clinics are in use every day except Saturday afternoons. Two thousand patient treatments are given each month in the general clinic (for teaching) and 1,000 in the private clinic.

The students, interns, residents, and departmental staff examine patients in the general clinic. The delivery rooms are open at all times to our medical students and house staff.

WILLIAM J. DIECKMANN, M.D.

Department of Reviews and Abstracts

Selected Abstracts

Pregnancy, Physiology, Diagnosis

Buxton, Russel: False Negative Results in the Friedman Test for Pregnancy, *Virginia M. Monthly* 71: 303, 1944.

Reports of negative Friedman tests have been found accurate in only 70 per cent of patients followed up at the Buxton Hospital since 1940. In 34 tests, the total number of errors was eight. In one the wrong urine was brought in for testing, in another the urine was collected in the afternoon, and in two others no cause for error could be ascertained. Four false negatives were found in patients who were taking estrogen therapy. These cases are reported in detail. As further confirmation of the fact that estrogen will induce a false negative test in the presence of pregnancy, a patient was selected who was known to be pregnant. A positive Friedman test was obtained and then the patient was placed on 40,000 units of Theelin in 7 days. The test became negative under estrogen therapy but the pregnancy persisted.

WILLIAM BICKERS.

Beruti, J. A., Leon, J., and Tenconi, E.: New Contribution to the Study of Transverse and Oblique Positions With Special Reference to Their Roentgen Diagnosis, *Prensa méd. argent.* 30: 2003, 1943.

The authors observed 14 cases: 11 transverse and 3 oblique. They show that the classic concept that in the transverse position the back of the fetus is always directed anteriorly or posteriorly is incorrect.

To avoid confusion, the authors accept the eight following varieties: anterior, anterosuperior, anteroinferior, posterior, posterosuperior, posteroinferior, superior and inferior.

Roentgen diagnosis is easy for the pure superior and inferior varieties, and the length of the images of the ribs passing beyond the vertebral column may reveal the degree of rotation of the fetus on its longitudinal axis. It is claimed by some that the anterior or posterior position of the back cannot be recognized. But if two films are taken, one in normal and the other in oblique exposure, it is easy to make the differential diagnosis.

Five of the 11 transverse positions were of the dorsosuperior variety. It seems that puriparity plays an important part in the etiology of this variety. The tendency to spontaneous change and the ease with which external version is performed are especially notable in the dorsosuperior variety and this applies also to the anterosuperior and posterosuperior ones. This explains why these varieties have been so seldom recognized clinically in the course of labor. On the other hand, spontaneous transformation of the transverse position into a longitudinal one never occurs in the frank dorso-anterior and dorsoposterior varieties.

The prognosis of the varieties in which the transverse position is corrected is favorable, provided that there is no anomaly in the pelvic canal. If the dorso-superior position persists, the mother runs the risk of premature rupture of the membranes, and prolapse of the cord is frequent and increases greatly the fetal mortality. When some mechanical obstacle is the cause of the dorso-anterior or dorsoposterior position, internal version and especially extraction by the natural route are made difficult and the fetal mortality is high; abdominal cesarean section is indicated in these cases.

The obstetrician must know the different varieties to guide him in performing internal version: he must bring down the lower foot in a dorso-anterior position, the upper foot in a dorsoposterior and the anterior foot in a dorsosuperior.

In any oblique presentation, the back of the fetus may offer eight different varieties as in the transverse presentation.

J. P. GREENHILL.

Chavanne, F. C., and Pittaluga, L.: Multiple Pregnancy, *Semana méd.* 50: 543-547, 1943.

The authors reviewed 257 multiple births observed in 18,129 labor cases seen at the Instituto de Maternidad of Buenos Aires from 1934 to 1942. There were 252 twin births and 5 triplets; i.e., twins occurred once in 72 births and triplets once in 3,626. One hundred thirty-two of the mothers were Argentinians, 125 were foreign. There were 88 primiparas and 169 multiparas. Among Argentinian women, twins occurred most often from age 20 to 25, and among foreign women (mostly Spanish and Italian) from 30 to 35 years. Two of the 257 patients died, a maternal mortality rate of 0.78 per cent. One of these deaths was due to amniotic infection, but the other was due to meningitis which was present before the onset of labor. In five instances, multiple pregnancy was repeated in the same mother. Forty per cent, or 109 women, were members of prolific families, with at least five brothers and sisters. Only six were nonsiblings. Family histories showed multiple pregnancies in 12 per cent, but this figure is believed to be lower than the actual number, because many women ignore the presence of twins in their family and even more in their husband's family.

Twin pregnancies are accompanied by more complications than single ones. There is greater distention of the abdomen, frequent hydramnios, and frequent edema, and above all, greater frequency of toxemia. In 17,862 single pregnancies toxemia occurred in 454, or 2.54 per cent, while in 257 multiple pregnancies, there were 26 cases of toxemia, or 10 per cent. The incidence of eclampsia in the first group was 0.34 per cent, while in the 257 multiple pregnancies, there were three cases, or 1.16 per cent.

In the 17,862 single pregnancies, 87 per cent were at term, while only 40 per cent of the multiple pregnancies were at term. The proportion of stillbirths was twice that of single pregnancies; 8 per cent contrasted with 4 per cent. In the 252 twin births, presentation of both fetuses was cephalic in 41.27 per cent; one cephalic, the other podalic, in 40.4 per cent; both podalic, 8.33 per cent; one cephalic, one shoulder, 3.9 per cent; one podalic, one shoulder, 2.7 per cent; and both transverse, 0.39 per cent. Forty-one operations, or 15.95 per cent, were required, contrasted with 6.15 per cent in single births. Of the 41 cases, five were forceps deliveries, 32 internal versions, two cephalic embryotomies and 18 pelvic extractions. There were 504 infants, 265 boys and 239 girls. In 169 births, both infants were of the same sex and 83 of different sex. Excluding stillbirths, 99 had died after two weeks, an infant mortality of 20.6 per cent.

In the 257 cases, the puerperium was normal in 70 per cent, subfebrile in 23 per cent and febrile in 7 per cent. These percentages are approximately the same as for single births, except for a slight increase in subfebrile puerperia.

J. P. GREENHILL.

Dragiff, David A., and Karshan, Maxwell: Effect of Pregnancy on the Chemical Composition of Human Dentin, *J. Dent. Research* 22: 261, 1943.

This study attempts to ascertain whether pregnancy has any effect on the ash, calcium, and phosphorus contents of the dentine of human teeth. Without selection, 31 teeth were extracted from pregnant patients at the Vanderbilt Clinic, and the teeth of the control group, 21 in number, were from nonpregnant females in approximately the same age group. A modification of the Shear and Kramer method was employed. A modification of the Fiske and Subbarow method was used for the phosphorus determination.

The results of the analysis indicated that no difference exists between the pregnant and nonpregnant group with respect to the calcium, phosphorus, and ash content of teeth. The authors conclude that there is no basis for the view that minerals are withdrawn from the teeth of human beings during pregnancy.

There is a brief but adequate review of experimental and clinical observations which reveals a difference in the conclusions regarding the relationship between pregnancy and the teeth.

HOWARD C. MOLOY.

Weisman, Abner I., and Coates, Christopher W.: **The Frog Test (*Xenopus laevis*) for Pregnancy**, West. J. Surg. 52: 171, 1944.

The South African frog (*Xenopus laevis*) is really not a frog. It is an "Anuran amphibian." The female has the peculiar biologic habit of carrying the eggs throughout the year and extruding them only at mating, or after hormone stimulation.

Four ounces of concentrated morning urine in each patient is required. To 80 c.c. of urine twice the volume of acetone is added. The mixture is stirred and allowed to stand when the precipitated proteins and hormones will have settled to the bottom. The supernatant fluid is decanted, the residue dried and mixed with 3 c.c. of tap water and adjusted to a pH of 5.5. One cubic centimeter is injected in the dorsal lymph space. A positive test is connoted by extrusion of the eggs usually about 8 hours after injection. The accuracy is 98.9 per cent for diagnosis of early pregnancy.

WILLIAM BICKERS.

Sullivan, Charles: **Diet in Pregnancy**, New England J. Med. 230: 167, 1944.

It is the responsibility of the physician conducting prenatal care to make every effort to insure the physical stamina and constitutional adequacy of the newborn infant.

Eugenically, the parturient state calls for the very best from a nutritional standpoint that the civilized state can present, so that the growing fetus will have available the maximum and optimum material essential to assure generations free from anomalous deficiencies of growth, as in the teeth, female pelvis and so forth, without extracting too great a toll from the parent host.

The daily dietary requirements of the average woman are reviewed, and a basic list is presented of food elements that with minimal supplemental additions will provide for an adequate normal nutritive relation between the pregnant woman and the fetus.

JAMES P. MARR.

Pregnancy, Complications

Kunz, Arturo Carlos: **A New Treatment of Eclampsia**, Bol. Soc. de obst. y ginec. 22: 570-575, 1943.

A new treatment of eclampsia with "Derifilina," a compound of theophylline and oxyamine, is reported by the author. Its rationale is based on the theory that the eclamptic state results from angiospasm, producing in turn edema and cerebral ischemia, which is the direct cause of convulsions. "Derifilina" is a white crystalline powder easily soluble in water. The combination increases the effects of its two components; the dominantly diuretic action of theophylline through renal vasodilatation and its vasodilating action on coronary, cerebral and pulmonary vessels is compensated by oxyamine which suppresses the usual abrupt effects of theophylline on arterial tension. "Derifilina" has a double vascular action, direct peripheral vasodilatation and on the vasomotor centers. In patients it produces (1) a short period of hypotension; (2) a slight increase in pulse amplitude; and (3) after two to three hours a further slight hypotensive effect with diminution of the pulse wave which lasts several hours.

The classic Stroganoff treatment of eclampsia is essentially antispasmodic, but with less pronounced effect than that produced by "Derifilina." The author reports spectacular results in four cases. The drug (one ampule) was administered intravenously in 20 c.c. of hypertonic glucose solution. The effect is immediate. Even during injection the blood pressure may fall from 23 or 24 c.c. of Hg to 7½, 8 or 9 c.c., and convulsions cease immediately. Only in two cases did slight convulsions recur within five minutes of the injection. In three cases, treatment was continued with the classic Stroganoff technique which had been begun on admission and 0.015 gr. of morphine hydrochloride served to maintain the effect of "Derifilina." Injection was not repeated in any case because it was unnecessary. The author believes that cure might be obtained with repetition of the drug, without following the Stroganoff method, but prefers the combina-

tion, since the latter does not require the vigilance necessitated by the stronger drug. Blood pressure returned to 11 or 12 and remained at this level for 24 hours.

In the three cases whose treatment was continued with the Stroganoff method, contractions began and spontaneous parturition occurred 8 to 16 hours after initiation of treatment. In no case was it necessary to shorten labor by intervention, since the patient's condition indicated that normal delivery could be accomplished. The excellent results obtained with this treatment are the more remarkable because two of the four patients were in extremely serious condition; in one the level of uric acid in the blood was 80 mg., and in the other 114 mg., which generally indicates a fatal prognosis.

J. P. GREENHILL.

Araujo, J. Onofre: *Present Aspects of the Problem of Eclampsia*, Rev. de ginec. e d'obst. 37: 143-164, 1943.

The author states that of the three elements which accompany eclampsia (edema, hypertension and albuminuria, or better still proteinuria) the most constant and perhaps the only one is arterial hypertension. According to Irving and Eastman among others, it depends on generalized arteriolar spasms, demonstrated by the correlation between the pressure values and the examination of the retinal vessels.

The author discusses the gravidic factors of hypertension, dividing them into metabolic and neuro-endocrine. This discussion reveals one outstanding fact: the intimate connection of pregnancy toxemia of the last trimester with the hypertensive syndrome. All authors agree that the cause of the convulsive crisis is cerebral edema.

The treatment of eclampsia and of the hypertensive syndromes which occur in the gravido-puerperal cycle is best based on the classification of these clinical entities proposed in 1940 and accepted by the American Committee. Any hypertension beginning before the twenty-fourth week of pregnancy should be considered as not having its etiologic cause in pregnancy, and a systolic pressure of 140 with a diastolic one of 90 should be accepted as the limit of normal in the pregnant woman.

The prognosis must be considered from the fetal and maternal points of view. For the fetus, pregnancy toxemia is one of the most frequent causes of death, being exceeded only by syphilis.

The cause of death in eclampsia is myocardial insufficiency, acute edema of the lungs and pneumonia, in addition to cerebral and meningeal hemorrhage.

The best methods to evaluate the intensity of the toxemia are regular taking of the arterial pressure and examination of the fundus of the eyes. Wagener, studying the arterioles of the retina in pregnancy toxemia, demonstrated four consecutive phases: spastic narrowing of the arterioles, irregular constriction of the arteries, appearance of hemorrhagic foci, and of whitish spots and diffuse retinosis. When the arterial pressure is above 140 mm., 72 per cent of the patients show evident changes in the retinal arterioles: hemorrhagic foci suggest danger of permanent lesion and justify interruption of pregnancy.

The treatment of the hypertension and of the convulsions must be considered separately. That of the former may be medical, surgical or obstetric, while that of the latter must consist of combating the cerebral edema, detoxifying the organism if possible and providing rest for the sensorium. To reach this triple end, hypertonic serums, venesection and sedatives are used.

J. P. GREENHILL.

Fuster, M. Fernandez: *Experimental Eclampsia*, Bol. Asoc. méd. de Puerto Rico 36: 109-113, 1944.

A convulsive syndrome which cannot be distinguished from eclampsia was induced by Fuster in a nontoxemic primigravida by the injection, intravenously of 800 c.c. of a 10 per cent solution of sodium chloride. The author believes that this is the first time this has been accomplished. Based on this experiment and on various observations by several workers, he concludes that the signs and symptoms of the toxemias of late pregnancy are due to a retention of sodium chloride in the tissues in a higher concentration than is compatible with normal

physiologic processes. The convulsions are probably due to the irritating effect on the brain of the high salt concentration.

The author does not know the cause of the abnormal retention of sodium chloride, but he suggests as a possibility the action of placental hormones and/or of the adrenal cortical hormones.

J. P. GREENHILL.

Toxemia

Gonzales, J. B.: Puerperal Fever Postpartum Infection of the Genital Canal, *Semana méd.* 50: 1197-1206, 1943.

The author outlines the history of puerperal fever and theories concerning it and stresses that there has been too much interference with the natural defenses in management of this condition. He deplores the use of antiseptics, which have yielded, at best, only mediocre results. These unsatisfactory practices he attributes to faulty thinking that infection should be controlled from without, whereas, if natural function of the body is to be utilized, it should be controlled from within.

The author says that the concept of universal value of the defenses of the body is quite different from that of recognition of the existence of natural defenses, which forms the basis of a theory of absolute noninterference, recognizing that they never fail, that they always are efficient and that these never should be substituted by other agents. This does not mean that these defenses are always sufficient to repel a bacterial invasion, but it does mean that there is no superior method; it means that any treatment applied from without it not only useless, but harmful; it means furthermore, that any treatment applied from without will be inferior to that of autodefense, so that the prime condition must be that its action is not interfered with, and finally it means that almost always, but not always (from the medical standpoint) the result of natural defenses is to re-establish a healthy state. This fact is amply proved in practice, when the natural defenses are respected and adequately controlled.

J. P. GREENHILL.

Armand, M. F.: Early Rising in the Puerperium, *Obst. y ginec. latino-am.* 1: 688-698, 1943.

Armand is an advocate of early rising in the puerperium. An analysis of 200 cases in Haiti showed that early getting up prevents thrombosis and embolus, aids uterine involution, helps drainage of the lochia and fosters quick recovery of the patient. The author also employed early rising after such complications as hemorrhage from placenta previa, uterine atony and also after intrauterine manipulation. He did not observe a single case of inversion, prolapse or retroversion due to the early rising. He, therefore, strongly recommends early rising in the puerperium regardless of the type of delivery and the presence or absence of complications.

J. P. GREENHILL.

Gabastou, J.: Sulfonamide Therapy by the Transplacental Route, *Semana méd.* 50: 983, 985, 1943.

The author has reported six cases of sulfonamide therapy by the transplacental route. The technique consists of injection of 100 c.c. of 5 per cent protosil into the vein of the cord ten or fifteen minutes after labor. The cases were selected according to rigid indications, i.e., they exhibited a definite state of intrapartum infection, and they had not received previous sulfonamide medication. Patients with premature rupture of the sac, or with prolonged labor, or in whom operative interference appeared necessary, as a prophylactic measure, received treatment either orally or parenterally, but not by both routes simultaneously.

The transplacental route was selected for patients showing severe infection, in order to produce a topical reaction. They all had a temperature of 39° C., tachycardia, dry skin, fetid vaginal secretions, and in some instances, evidence of

infection in the blood stream. All patients displaying these severe symptoms, who were treated with sulfonamide transplacentally, showed remission of sepsis and were dismissed from the hospital as soon as patients with a normal puerperium.

J. P. GREENHILL.

Salm, R.: The Occurrence and Significance of *Clostridium Welchii* in the Female Genital Tract, J. Obst. & Gynaec. Brit. Emp. 51: 121, 1944.

The author made 843 vaginal swabs during the puerperium on patients showing a rise of temperature above normal. *Cl. welchii* was isolated on 50 cases or 6 per cent. In 300 swabs from venereal disease cases, *Cl. welchii* was isolated in 7.67 per cent, and in 300 swabs from pregnant women undergoing treatment for leucorrhea, *Cl. welchii* was isolated in 6.33 per cent. Forty per cent of *Cl. welchii* cases belonged to the category of manual and instrumental interference. None of the patients died or was seriously ill. *B. coli* was present in 62 per cent, anaerobic streptococci in 34 per cent and hemolytic streptococci in 10 per cent. It appears likely that the origin of *Cl. welchii* and *B. coli* is from the bowel itself.

The incidence of *Cl. welchii* increases with the number of examinations and instrumentations, and it appears likely that some of these organisms can be introduced with medical supplies such as instruments, cotton, etc. In the absence of clinical signs, active treatment should not be instituted without clinical evidence that invasion has taken place.

WILLIAM BERMAN.

Lubin, S., and Horowitz, I.: Postpartum Hematomas, Am. J. Surg. 63: 272, 1944.

In reporting 4 cases of postpartum hematomas, the authors call attention to the seriousness of the condition if not recognized and treated early. They describe 2 types, the immediate and the delayed, either of which may involve the perineum, labia, vagina, base of the broad ligaments, and even the subperitoneal tissues to the kidney and diaphragm. The cause is necrosis of blood vessels as the result of pressure, tears, and inadequate hemostasis. Immediate evacuation of the hematomas in conjunction with measures to combat shock is the treatment of choice in most cases. All of the authors' case reports were of involvement of the vulva, vagina, labia, or perineum. The literature is reviewed.

FRANK SPIELMAN.

Timberman, H. J.: Postpartum Appendicitis, Am. J. Surg. 55: 138, 1942.

The author calls attention to the rarity of appendicitis in the puerperium and reports 2 cases. These were the only ones observed in 17,489 deliveries from 1916 to 1939 inclusive. The symptoms and pathologic findings were typical. Both cases reported followed the administration of strong cathartics.

FRANK SPIELMAN.

Bloom, O. H.: Suppression of Lactation by Stilbestrol, Am. J. Surg. 54: 443, 1941.

Stilbestrol was administered to 110 postpartum patients in order to obtain a suppression of lactation. The dosage utilized was 5 mg. of the preparation 3 times daily for 2 days. No other form of therapy was used; no restriction of fluids, tight binder, atropine, saline cathartics, etc. Successful suppression of lactation was achieved in over 90 per cent of the cases. No untoward effects were noted.

FRANK SPIELMAN.

Miscellaneous

Henry, Noel R.: The Rh Factor and Prognosis, M. J. Australia 2: 114, 1944.

The author reports a case of a woman whose first infant died on its thirteenth day of life from jaundice after having had several blood transfusions. In the next two years this woman had three miscarriages at three months, five months, and two months. No further pregnancy ensued for the next six years. The patient then became pregnant for the fifth time. She was given progesterin and wheat germ oil.

She delivered a normal baby without any complications. The mother's blood belonged to group O and was Rh negative. The infant's blood was of group O and was Rh positive. (The father had to be Rh positive.) The author questions the significance of the six years of infertility, and feels that our knowledge is as yet incomplete to advise these women against future pregnancies.

WILLIAM BERMAN.

Simmons, R. T., Graydon, J. J., and Hamilton, Patricia: The Rh Factor in the Blood of Australian Aborigines, M. J. Australia 1: 553, 1944.

The authors collected blood samples from 281 pure-blooded Australian aborigines and four hybrids and these were all found to be Rh positive. The finding of the Rh factor in all pure-blooded Australian aborigines completes another link in the blood similarities of American Indians and Australian aborigines. The original stock of each race probably possessed only two blood groups, A and O, and all persons of group A belonged to subgroup A₁. The main difference in the blood of these two races is that the Australian aborigines have the highest, and the American Indians almost the lowest, type N percentages yet found.

WILLIAM BERMAN.

Necrology

LYLE G. McNEILE, M.D., obstetrician and gynecologist, of Los Angeles, California, died there March 1, 1945, at the age of 60 years. A graduate of the University of California in 1910, he established the Los Angeles Maternity Service, a maternity service of the city's health department, and was among the first members of the faculty of the University of Southern California when the Department of Obstetrics was organized in 1931, serving as instructor and professor until 1939. Dr. McNeile was a Fellow of the American College of Surgeons and a Diplomate of the American Board since 1930, but was retired from active practice.

HILLIARD EVE MILLER, M.D., obstetrician and gynecologist, brother of the late Dr. C. Jeff Miller, died April 20, 1945, at his home in New Orleans, Louisiana, of heart failure, at the age of 52 years. Born in Winchester, Tennessee, Sept. 25, 1893, he took his medical degree at Tulane University and served internships at the Charity Hospital, New Orleans, and the New York Lying-In Hospital. He entered the Medical Corps of the Army during World War I as first lieutenant. On his return to civil life he became instructor in obstetrics and gynecology at Tulane until 1924, then assistant professor until 1936, and then professor and head of the department until his retirement a year ago.

Dr. Miller was a member of his State and National Societies, The American College of Surgeons, The American Gynecological Society, Gynecological Travel Club (President), Southern Medical Association, New Orleans Obstetrical Society, and others.

Correspondence

Continuous Caudal Analgesia

To the Editor:

In the Dec. 30, 1944, issue of the *Journal of the American Medical Association*, Dr. Robert A. Hingson gives an interim report on caudal analgesia from a number of clinics. In it there are the following statements:

"This study compares so favorably with all other forms of pain relief in obstetrics that its significance is self-evident; the fetal mortality in this group has been 1.7 per cent as compared with the fetal mortality in the death registration area of the United States of 5.2 per cent. Out of these 42,000 cases there have been sixteen maternal deaths. Six were attributed to obstetric complications, seven to the misuse of caudal analgesia in unskilled hands and three may be considered anesthetic deaths—emphasizing the small permanent hazard to the mother associated with this form of pain relief."

Only six maternal deaths due to obstetric complications out of 42,000 cases is an amazingly low mortality, and should be elucidated as to how caudal analgesia produced that result. Why should there be three anesthetic deaths if the women had caudal analgesia? Seven women did lose their lives due to caudal analgesia, and how many more paid the penalty in other institutions whose deaths were not publicized?

The 5.2 per cent fetal mortality is the gross uncorrected mortality rate from all sections of the United States not only from the large clinics. Is the 1.7 per cent fetal mortality in this series also the gross uncorrected mortality or is it the mortality attributed to labor and delivery only? The comparison should be made for each institution between the caudal series and the other methods of analgesia and anesthesia.

"Parturients in whom fear can be controlled by confidence in their physician and in their surroundings are the ideal ones for the use of continuous caudal and spinal analgesia."

This class of patients does not need caudal analgesia, all they need is some morphine to ease the pain of the first stage of labor and ether at the time of delivery.

"Parturients in whom fear is uncontrolled can still be more satisfactorily managed with amnesia and general anesthesia."

If that is the case, then caudal analgesia loses all its attraction, for it is the nervous, hysterical and temperamental woman in labor that we are searching for a means to quiet. If we cannot use it on her, then the level-headed type does not need caudal analgesia and should not be subjected to it.

MORRIS LEFF, M.D.

NEW YORK, N. Y.

JANUARY 10, 1945.

Reply by Dr. Hingson

To the Editor:

The paper published as an interim report on caudal analgesia by me in the Dec. 30, 1944, issue of the *Journal of the American Medical Association* is at present out of date by recent experience, since this paper includes only an analysis of cases up to May 1, 1944.

Already 50,000 deliveries under continuous caudal analgesia have been reported to the Graduate Medical Course of the Philadelphia Lying-in Hospital by physicians who have completed the course and by physicians who have managed large groups of cases without training. In this compilation, there have been 19 maternal deaths which will be adequately considered in a forthcoming scientific paper to the profession. The comparison of fetal mortality from all sections of the United States with the fetal mortality in this reported series was made under identical conditions. It is the gross and uncorrected fetal mortality for both groups, which include hospital and nonhospital deliveries from all sections of the Country.

The last two questions raised may be answered by pointing out that Dr. Leff has not considered the welfare of the baby in either question. The day is past when women in labor are managed with morphine and ether without regard to their welfare. We now recognize the dual responsibility of selecting the form of management for the patient that is most satisfactory and the safest for her and her newborn baby.

ROBERT A. HINGSON, Surgeon
U. S. Public Health Service.

JANUARY 15, 1945.

Items

American Board of Obstetrics and Gynecology

Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted at Atlantic City, New Jersey, by the entire Board from Wednesday, June 13, through Tuesday, June 19, 1945. The Hotel Shelburne in Atlantic City will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for *re-examination* in Part II must make written application to the Secretary's Office not later than April 15, 1945.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1946 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

PAUL TITUS, M.D.

Announcement

In compliance with the directives imposed by the War Production Board limiting the amount of paper consumed in the production of this JOURNAL, the publishers find it necessary to change the format. As soon as these restrictions are lifted the original format will be restored. Even though the number of pages has been reduced, the actual content of the JOURNAL has not been decreased to any appreciable extent.

